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RELATION OF SERUM CALCIUM TO PATHOLOGIC CALCIFICATIONS OF HYPERVITAMINOSIS D

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The mechanism by which the calcifications of hypervitaminosis D are produced is largely of interest because of the information which may be gained from its study regarding many rather complex features of the calcium metabolism. Once the calcifications are regarded as the result of the precipitation of calcium salts from the serum rather than as the aftermath of the toxic effect of the vitamin on the tissues, the scope of this field of research is enormously increased. The present contribution is concerned with a study and interpretation of the evidence obtained by correlating the changes in the tissues with the serum calcium curves of animals during the time immediately following the administration of one single massive dose of activated ergosterol.

MATERIAL AND METHODS

Forty-eight rats and five rabbits were used in the experiments, and these were divided into four series.

Series 1 consisted of seven rats. Two were used as controls, and five were each given 0.4 cc. of activated ergosterol¹ 10,000 × at the beginning of the experiment.

Series 2 consisted of five rabbits, each of which received 2.5 cc. of activated ergosterol 10,000 × at the beginning of the experiment. They were killed at different intervals up to ninety-six hours. Determinations of blood calcium were made, not only immediately before death but also throughout the course of the experiment.

Series 3 consisted of thirty-one full grown male rats, four of which were used as controls. The remainder each received 0.5 cc. of activated ergosterol 10,000 × at the beginning of the experiment. These animals were killed at close intervals, the last group being killed one hundred and twelve hours after the beginning of the experiment.

Series 4 consisted of ten young male rats of an average weight of approximately 150 Gm. Two were utilized as controls, and the remainder each received 0.75 cc. of activated ergosterol 10,000 × at the beginning of the experiment. They were killed at intervals up to seventy-two hours.

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1. Footnote deleted.

In all series the animals were fed on stock laboratory diets. In addition to their regular diet the rabbits each received 15 grains (0.97 Gm.) of calcium lactate per day, which was administered in their drinking water. The activated ergosterol was administered to the rats with their food, and to the rabbits by introducing it into their mouths with a dropper. The animals were killed in all cases by ether anesthesia. Blood for calcium determinations was taken from the rabbits by cutting small vessels in the ear and allowing the blood to flow into a tube. It was obtained from the rats, while they were under anesthesia, by cutting the tail and allowing the blood to escape into a tube. If 5 cc. could not be obtained by this procedure, recourse was taken to a cardiac puncture. At autopsy, blocks were taken from the heart, aorta, lung, liver, spleen, kidney, parathyroid and thyroid. The incisor teeth were also removed for study and will be reported on separately. Because of the inaccuracy of the usual methods of staining for calcium (Cameron²) the tissues in series 1 and 2 were fixed in alcohol and a solution of formaldehyde in order to prepare sections for incineration (Policard³). Estimates of serum calcium were made by the Collip and Clark modification of the Tisdall-Kramer method. The serum was prepared by incubating the blood for

OBSERVATIONS

TABLE 1.—*Observations in Series 1*

Rat	Serum Calcium		Calcification of Coronary Vessels	Calcification of Aorta
	Hours After Receiving Ergosterol	Before Death, Mg. per 100 Cc.		
1.....	0	8.9	Negative	Negative
2.....	0	8.6	Negative	Negative
3.....	18	12.2	Negative	Negative
4.....	24	14.4	Negative	Negative
5.....	30	15.9	Negative	Negative
6.....	48	17.6	Slight	Slight
7.....	72	16.1	Positive	Positive

half an hour at 37 C., after which the clot was loosened by an applicator and the tube placed in an icebox for two hours. After centrifugation at high speed the serum was pipetted off and the calcium estimation made.

SERIES 1.—*Microscopic Examination.*—Sections from both the rats used as controls and the test rats killed early in the experiment showed considerable variation in the color and intensity of the hematoxylin staining. Furthermore, there was present in both the control and the experimental rats some degree of vacuolation in the cellular areas between the elastic plates of the aorta. In the stained sections no definite lesions were found in the aorta until the sections from rat 7 were examined, and they showed the lesion typical of hypervitaminosis D in that location. In the early specimens the sections of cardiac muscle showed some variability in staining qualities, and in rat 6 a slight infiltration by inflammatory cells was noted about one of the branches of a coronary vessel. No areas of calcification as depicted with hematoxylin were noted in the sections from rat 6. Rat 7 showed areas of marked deposition of calcium in the sections from both the aorta and the heart. There were also many areas of infiltration of the cardiac muscle by inflammatory cells. These were usually situated about the smaller branches of the coronary vessels. The series of sections which were

2. Cameron, J. R.: J. Path. & Bact. **33**:929, 1930.

3. Policard, A.: Protoplasma **7**:464, 1929.

incinerated showed no increase of mineral content in the aorta or heart until the sections from rat 6 were examined; these showed a slight but definite increase in mineral in the inner third of the media in some areas. Sections from the heart of rat 6 showed the walls of small branches of the coronary vessels to contain more mineral than was usual in the preceding sections. The sections from rat 7 showed marked amounts of mineral matter in both the aorta and the heart in the locations described.

Correlation of Pathologic Changes With Estimations of Serum Calcium.—After the administration of the activated ergosterol the serum calcium level ascended for approximately forty-eight hours and then began to fall. Calcifications first appeared when the peak of the curve had been reached, but were not prominent until the curve had begun to fall. Thus the appearance of marked calcifications in the tissues was associated with the beginning of the fall of the serum calcium curve.

SERIES 2.—Microscopic Examination.—All the rabbits, with the exception of rabbit 5, showed calcifications of recent origin in the inner third of the aortic media. In the stained sections swollen areas situated between adjacent elastic plates were evident in the inner third of the media. In these areas a considerable

TABLE 2.—*Serum Calcium Levels in Series 2*

Rabbit	Mg. of Calcium per Hundred Cubic Centimeters of Serum at Given Number of Hours After Rabbit Received Ergosterol				
	0	24 Hours	48 Hours	72 Hours	96 Hours
5.....	16.4	15.5*			
6.....	14.0	13.8	17.1	14.5*	
7.....	15.0	14.4	15.4	18.8	14.3*
8.....	13.4	13.3	13.3*		
9.....	14.0	16.1	13.3	11.5*	

* Postmortem examination made.

amount of material staining a deep blue was encountered, some of which was associated with elastic fibers; other portions of it were related to the cells of the areas between adjacent elastic plates, and some of it was amorphous. The edematous nature of the area in which the deposition of calcium occurred was striking, and was apparently of sufficient importance to cause a compression of the cellular areas between the adjacent elastic plates. The incinerated sections of the aorta showed the described areas to contain greatly increased amounts of mineral matter. The sections of cardiac muscle showed some calcification of muscle, but the small branches of the coronary vessels did not show the extensive lesions seen in the hearts of the rats.

Correlation of Pathologic Changes With Estimations of Serum Calcium.—The response of the serum calcium to the administration of activated ergosterol was exceedingly variable in the rabbits. In two, rabbits 5 and 8, there was little change of significance, yet recent calcification was very obvious in the aorta of rabbit 8. In rabbit 6, there was little change for the first twenty-four hours, but a marked upswing occurred in the second twenty-four hours and a marked downswing during the third twenty-four hours. In rabbit 7 the great part of the upswing occurred in the period between forty-eight and seventy-two hours after the administration of the ergosterol, and then a marked drop occurred between this time and ninety-six hours. In rabbit 9, a rather mild upswing occurred in the first twenty-four hours, and this was followed by a drop which lasted for the next

forty-eight hours and carried the serum calcium far below its original level. As all the animals, with the exception of rabbit 5, showed recent calcifications in the aortic wall, it is obvious that calcium was deposited in the tissues when the serum calcium level had shown either little change or a marked rise followed by a fall.

TABLE 3.—*Observations in Series 3*

Rat	Hours After Receiving Ergosterol	Serum Calcium Before Death, Mg. per 100 Cc.	Calcification in Heart and Coronary Vessels	Calcification in Aorta
1.....	0	0.8	Negative	Negative
2.....	0	9.8	Negative	Negative
3.....	0	10.6	Negative	Negative
4.....	0	10.9	Negative	Negative
5.....	16	11.2	Negative	Negative
6.....	16	11.0	Negative	Negative
7.....	16	12.9	Negative	Negative
8.....	24	12.1	Negative	Negative
9.....	24	12.1	Negative	Negative
10.....	24	13.0	Negative	Negative
11.....	40	13.0	Negative	Negative
12.....	40	13.0	Negative	Negative
13.....	40	13.6	Negative	Negative
14.....	48	13.0	Negative	Negative
15.....	48	15.5	Negative	Negative
16.....	48	15.9	Negative	Negative
17.....	64	14.9	Negative	Negative
18.....	64	15.1	Negative	Negative
19.....	64	14.7	Positive	Negative
20.....	72	16.3	Negative	Negative
21.....	72	17.0	Negative	Negative
22.....	72	12.2	Negative	Negative
23.....	88	14.5	Negative	Positive
24.....	92	16.1	Negative	Negative
25.....	92	12.6	Negative	Negative
26.....	92	12.4	Negative	Positive
27.....	113	13.7	Negative	Negative
28.....	113	13.9	Negative	Negative
29.....	113	13.4	Negative	Positive
30.....	113	Not done	Negative	Positive
31.....	113	14.4	Negative	Positive

TABLE 4.—*Observations in Series 4*

Rat	Hours After Receiving Ergosterol	Serum Calcium Before Death, Mg. per 100 Cc.	Calcification of Coronary Vessels	Calcification in Aorta	Inflammatory Cell Infiltration
1	0	10.3	Negative	Negative	Negative
2	0	10.3	Negative	Negative	Negative
3	24	10.0	Negative	Negative	Negative
4	24	13.0	Negative	Negative	Negative
5	48	17.4	Negative	Negative	Negative
6	48	16.3	Slight	Negative	Slight
7	72	17.0	Marked	Marked	Marked
8	72	14.7	Positive	Marked	Marked
9	72	15.3	Positive	Marked	Marked
10	72	Not done	Marked	Marked	Positive

SERIES 3.—*Microscopic Examination.*—The hearts and aortas of this series of rats were examined by means of both stained and incinerated sections. Only a few of the rat aortas revealed areas of calcification. Sections of the heart showed only rarely a calcified coronary vessel. There were mild infiltrations by inflammatory cells about the smaller coronary vessels in the cardiac musculature of several of the animals in the latter part of the series.

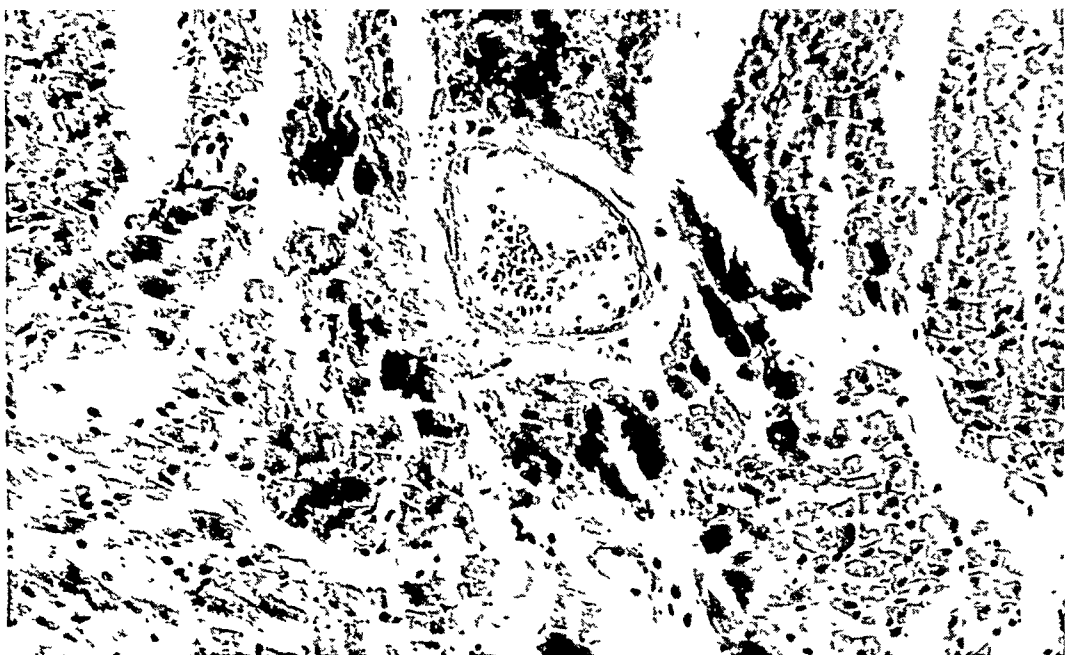


Fig. 1.—Photomicrograph of section of cardiac muscle from rat 10, series 4; hematoxylin and eosin stain; $\times 200$. The picture demonstrates marked calcification of the muscle with little evidence of infiltration by inflammatory cells.



Fig. 2.—Photomicrograph of section of cardiac muscle from rat 7, series 4; hematoxylin and eosin stain; $\times 120$. The picture shows a lesion demonstrating both marked calcification and infiltration by inflammatory cells. Calcification of the wall of the blood vessel is pronounced.

Correlation of Pathologic Changes With Estimations of Serum Calcium.—In this series of rats the highest calcium readings were found in those killed at the end of seventy-two hours. Up to that time the animals demonstrated a gradual rise in the calcium content of the serum and after that time a more or less irregular fall. The first animal to demonstrate calcifications showed a serum calcium level near the peak of the curve; in all the others the curve was on the downswing. It is significant that only some of these animals demonstrated lesions, and the lesions were not nearly so well marked as those of the next series to be described.

SERIES 4.—Microscopic Examination.—Although the sections from rat 6 showed evidences of slight deposition of calcium in the aorta and heart, marked lesions were not found until the sections from the last four rats were examined.



Fig. 3.—Dark-field photomicrograph of a calcified coronary vessel from rat 7, series 4; incinerated specimen; $\times 180$. The increased amount of mineral matter in the wall of the blood vessel may be seen against the black background.

Sections from the aortas revealed the lesions to be situated in the inner third of the media, and to present the same appearance as those already described in this paper and in a previous contribution (Ham⁴). The lesions in the cardiac musculature showed a certain variability in appearance. One type of lesion demonstrated marked calcification with little infiltration by inflammatory cells (rat 10, fig. 1). Another type illustrated a marked infiltration by inflammatory cells with only a moderate amount of calcium deposition (rats 8 and 9). A third type of lesion showed a marked amount of calcium deposition with a marked infiltration by inflammatory cells (rat 7, fig. 2).

Correlation of Pathologic Changes With Estimations of Serum Calcium.—In this series of animals the peak of the serum calcium curve appeared to be reached

4. Ham, A. W.: Arch. Path. 14:613, 1932.

in between forty-eight and seventy-two hours. In one instance slight calcification appeared at the end of forty-eight hours, but immediately after this time the calcifications became marked. Although some calcification was found at the time of the greatest hypercalcemia, deposits of calcium were found in much greater amounts after enough time had elapsed for the calcium of the serum to begin its fall.

It is significant that in general the activated ergosterol demonstrated a very constant effect in the three series of rats. Shortly after its administration the serum calcium began to rise, and a peak was reached in somewhere between twenty-four and seventy-two hours. It is unfortunate that estimations of calcium could not be made frequently from the same animals, but it is difficult to obtain even once sufficient blood for a calcium determination, particularly if young rats are used, and from these experiments and others which have been reported (Ham⁴) young rats appear to be affected to a greater extent than older ones. Rabbits are known to possess a very unstable calcium metabolism, and the results in this paper bear out this conclusion. Although in most instances a change in the level of the serum calcium occurred, in one instance calcifications were produced with little change in the serum calcium level; the significance of this observation will be discussed later in detail. It is also obvious that series 4 was the best, so far as this study is concerned, because sufficient ergosterol was given to cause marked, definite lesions in every instance in which the animal was allowed to live a sufficient length of time. In this work calcifications are regarded as stainable with hematoxylin, although we are well aware of the possibilities of error in this connection, but it is felt, because of previous work (Ham⁴), that this staining method is sufficiently reliable in this type of experiment, particularly when controlled with incineration.

COMMENT

Pathologic calcifications have been divided into two general types, those which are dependent on degenerative changes in the recipient tissues and those which are dependent on the inability of the serum and tissue fluid to retain all its calcium in solution (Ham^{5a}). Recognized examples of the latter type in man have been described by several authors, and it is known that in many instances they are associated with parathyroid tumors and in other instances with disease of the bone not associated with or caused by parathyroid tumors. The literature in this field has recently been reviewed completely by Barr.⁶ It is well known, moreover, that calcifications of this type have been pro-

5. Ham, A. W.: (a) Cartilage and Bone, in Cowdry: *Special Cytology*, ed. 2, New York, Paul B. Hoeber, Inc., 1932; (b) *Angle Orthodontist* 2:142, 1932.

6. Barr, D. P.: *Physiol. Rev.* 12:593, 1932.

duced experimentally by intraperitoneal and intravenous injections of calcium salts (Tanaka,⁷ Katase⁸), by the intraperitoneal injection of calcium gluconate (McJunkin, Tweedy and Breuhaus.⁹), by the injection of large amounts of parathyroid hormone (Hueper,¹⁰ McJunkin, Tweedy and Breuhaus⁹ and others), by the administration of massive doses of vitamin D (by a host of investigators) and by varying the reaction of a diet high in calcium in mice (by Rabl¹¹ and by Butler¹²).

It is therefore evident that calcium salts may be precipitated from the serum and tissue fluid into the tissues themselves. At first thought it may seem that this phenomenon is nothing more than the result of a hypercalcemia, but investigation has demonstrated this explanation to be inadequate. Shelling¹³ found that calcification of this variety occurred in parathyroidectomized animals when they were given sufficient phosphate in their diet. He also showed¹⁴ that the parathyroidectomized animals were more susceptible to the action of vitamin D in producing calcifications than were normal animals. In both these instances it is apparent that calcifications were produced without the advent of hypercalcemia. Smith and Elvove¹⁵ in their experiments with ergosterol poisoning found that on some occasions enormous deposits of calcium were associated with little change in the serum calcium level, whereas on other occasions marked increases of the serum calcium level were not associated with precipitations in the tissues. Furthermore, one rabbit in series 2 showed extensive calcifications with little change in the serum calcium level, whereas many of the rats in series 3 that showed considerable change in the serum calcium level showed little in the way of calcium deposits. It seems apparent that the hypercalcemia in itself is not sufficient to account for the calcifications—a conclusion already postulated by Smith and Elvove.

As the level of the serum calcium does not bear a definite or constant relationship to the precipitation of calcium salts into the tissues, it becomes evident that the state of the serum calcium must be investigated for the answer to the problem. The blood is known to contain more calcium than can be explained by the laws of simple solution. The factors in this phenomenon have recently been comprehensively

7. Tanaka, M.: *Biochem. Ztschr.* **35**:113, 1911.

8. Katase: *Beitr. z. path. Anat. u. z. allg. Path.* **57**:516, 1914.

9. McJunkin, F. A.; Tweedy, W. R., and Breuhaus, H. C.: *Arch. Path.* **14**:649, 1932.

10. Hueper, W.: *Arch. Path.* **3**:14, 1927.

11. Rabl: *Virchows Arch. f. path. Anat.* **245**:542, 1923.

12. Butler, M.: *Proc. New York Path. Soc.* **24**:79, 1924.

13. Shelling, D. H.: *Proc. Soc. Exper. Biol. & Med.* **28**:301, 1930.

14. Shelling, D. H.: *Proc. Soc. Exper. Biol. & Med.* **28**:303, 1930.

15. Smith, M. I., and Elvove, E.: *Pub. Health Rep.* **44**:1245, 1929.

reviewed by Peters and Van Slyke.¹⁶ There is evidence to show the existence of at least three fractions in the serum calcium: first, a relatively small portion which is held in solution by the forces which ordinarily govern solubility in salt solutions; second, a portion which is held in solution by the serum proteins, and third, a portion which is held in solution by unknown factors which appear to be greatly influenced by the presence of the parathyroid hormone. A certain amount of evidence indicates the portion of the serum calcium associated with the parathyroid hormone to be nondiffusible (Cameron and Moorhouse,¹⁷ Cameron¹⁸), although there is controversy on this point (Morgulis and Perley¹⁹). Furthermore, there appears to be a kind of equilibrium between the various fractions of the serum calcium and the calcium of the bones. The literature regarding this phase of the problem has been reviewed in previous contributions (Ham⁵).

There is now a considerable amount of evidence to indicate that vitamin D acts on the serum calcium level in a manner identical with that of the parathyroid hormone. The absence of either parathyroid hormone or vitamin D in growing animals results in rachitic changes in the growing zones of the long bones. The long-continued administration of either parathyroid hormone (Jaffe and Bodansky²⁰) or vitamin D (Grauer²¹) in huge doses results in a marked loss of mineral salts from the skeleton, and the bones in both instances demonstrate the changes characteristic of osteitis fibrosa cystica. Furthermore, large doses of either substance may result in the production of metastatic calcification. Although the action of vitamin D in parathyroidectomized animals is frequently discussed in the literature, it is probable that complete parathyroidectomies are extremely difficult to accomplish because of the widespread distribution of these glands. It is significant that the experiments of Taylor, Branion and Kay²² demonstrated the inability of large doses of vitamin D to raise the serum calcium levels of dogs sufficiently to prevent tetany after extraordinarily complete dissection of the neck, although the same dosages of vitamin D prevented tetany when the usual parathyroidectomy had been performed. There is therefore good reason to believe that vitamin D accomplishes its action on the serum level through the agency of the parathyroid gland,

16. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1931.

17. Cameron, A. T., and Moorhouse, V. H. K.: *J. Biol. Chem.* **63**:687, 1925.

18. Cameron, A. T.: *Canad. M. A. J.* **16**:759, 1926.

19. Morgulis, S., and Perley, A. M.: *J. Biol. Chem.* **88**:169, 1930.

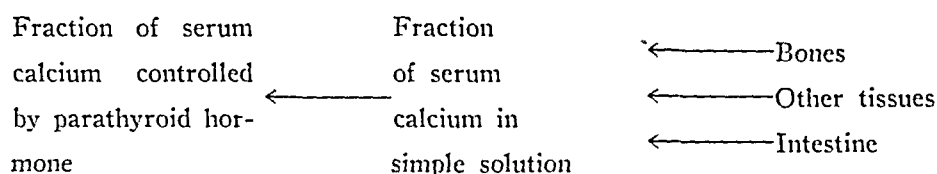
20. Jaffe, H. L., and Bodansky, A.: *J. Exper. Med.* **52**:669, 1930.

21. Grauer, R. C.: *Proc. Soc. Exper. Biol. & Med.* **29**:466, 1932.

22. Taylor, N. B.; Branion, H. D., and Kay, H. D.: *J. Physiol.* **69**: Proc. xxxv, 1930.

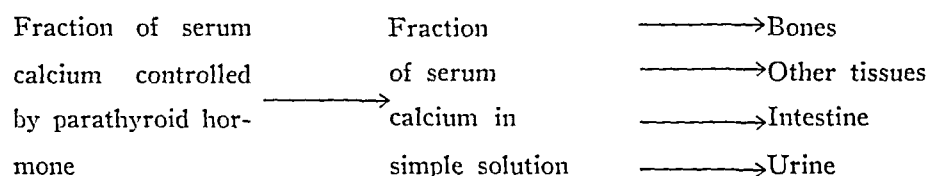
although it is also conceivable that it may act through the activation of the hormone rather than on the gland.

Consequently there is evidence to show that the calcifications associated with hypervitaminosis D depend on a precipitation of calcium from the serum, and furthermore that this precipitation is more dependent on the state of the serum calcium than on its level. As it is most probable that vitamin D exerts its effect on the calcium metabolism through the parathyroid mechanism, the calcifications associated with hypervitaminosis D can be explained as being dependent on the shifting about of calcium between the various fractions of the serum, the tissues and the intestine when the vitamin is administered in enormous amounts. As the appearance of the pathologic calcifications is associated with the downswing of the serum calcium curve following a single massive dose of the vitamin, it seems probable that the distribution of calcium in the various fractions in the serum is considerably changed throughout the course of a rise and fall in the serum curve induced by vitamin D. During the upswing, the shift in calcium toward the serum could be accounted for by the attraction of the increased amount of parathyroid hormone in the circulation or by its increased ability to attract calcium. The shift could be represented diagrammatically as follows:



Thus the amount of the serum calcium is increased at the expense of the bones, other tissues and calcium in the intestine.

After the height of the hypercalcemia is attained, the serum calcium begins to fall because the parathyroid hormone in the blood no longer exerts the same attraction for calcium. The release of calcium from this fraction of the serum calcium therefore induces a shift of the equilibrium in the other direction. This shift may be represented diagrammatically as follows:



As the serum retains only a small amount of the total serum calcium in simple solution, it is evident that if the release of calcium from the greatly increased fraction associated with the parathyroid hormone is at all rapid, precipitations of calcium salts will be forced, and although much of the liberated calcium is deposited in the bones or excreted by

way of the kidney or intestine, there is a distinct possibility of calcium salts being precipitated in the tissues.

Thus it is thought that the observations in this series of experiments indicate that the mechanism of calcification in hypervitaminosis D depends primarily on the release of calcium from the parathyroid hormone-controlled fraction of the serum calcium, so that the serum is unable to retain in simple solution the calcium thus liberated. Other factors, such as the phosphate content of the serum, the carbon dioxide tension and the physicochemical affinity of certain tissues for calcium salts, are concerned in the mechanism of calcification, but their action is dependent on the degree of saturation of the serum with calcium in simple solution. It also appears that the utilization of a single dose of vitamin D allows an excellent opportunity to study the problem, as it seems logical to consider the shift in calcium as occurring toward the blood and particularly toward the parathyroid hormone-controlled fraction on the upswing of the serum calcium curve, and in the reverse direction as the serum calcium level falls.

Barr⁶ and Peters and Van Slyke¹⁶ in their recent reviews considered the portion of the serum calcium associated with the parathyroid hormone to be physiologically active because of the therapeutic action of the hormone in tetany and its toxic action in excessive dosages. It is questionable, however, whether this conclusion needs to follow from their evidence. If the fraction of the serum calcium governed by the parathyroid hormone is in a kind of equilibrium with the fraction which is held in solution by the forces ordinarily governing solubility in salt solutions, and this fraction in turn is also in equilibrium with the calcium reservoirs (the bones and possibly other tissues), it is seen that the administration of parathyroid hormone can result in nothing more than a shift in calcium from the bones, tissues and intestine toward the parathyroid hormone-controlled fraction of the serum calcium, which will in this case be greatly increased. Thus one does not expect to see pathologic calcifications appearing as the shift occurs in this direction (while the serum calcium is rising, following a single dose). On the other hand, as soon as the serum calcium begins to fall, because of the gradually diminishing calcium-binding effect of the administered parathyroid hormone, one expects the portion of the serum calcium in simple solution to reach rapidly a saturated state, so that the further liberation of calcium from the parathyroid-controlled fraction will result in the deposition of calcium salts in the bones, and if the process is sufficiently rapid, in the tissues as well. In the experiments reported in this paper it is obvious that the deposition of calcium in the tissues occurred in the rats when the serum calcium curve had attained its peak and was beginning to fall, a time that would correspond with the release of calcium from the parathyroid-controlled fraction. Thus the so-called

toxic effect of parathyroid hormone can be explained without assuming the fraction of the serum calcium controlled by it to be physiologically active.

The evidence regarding the ability of the parathyroid hormone to relieve tetany is likewise not proof that the portion of the serum calcium associated with it is physiologically active. Its use in this condition is to increase the fraction of the serum calcium that it controls at the expense of the other calcium of the serum as well as that of the tissues, bones and intestine. Although its first effect may be a temporary lowering of the part of the serum calcium which is in true solution and physiologically active because of its ionization, it is obvious that equilibrium quickly becomes established at a higher level so that the amount of the serum calcium in simple solution shortly becomes increased. It is significant that it is not uncommon for the first dose of vitamin D in severe cases of clinical rickets to precipitate an attack of tetany, from which the patient soon recovers. Furthermore, the experimental procedure of temporarily increasing the depth of tetany by the administration of vitamin D has been reported on by Taylor,²³ although his explanation differs from the one just given.

It is therefore possible to explain the therapeutic and toxic effects of vitamin D and parathyroid hormone without assuming the portion of the serum calcium associated with the parathyroid hormone to be physiologically active. If one keeps in mind the possibility of the shift of calcium between the intestine, bones and tissues and the various fractions of the serum, it is possible to explain many of the complex and apparently paradoxical features of the calcium metabolism. The reason for the ability of the serum, under the influence of parathyroid hormone or vitamin D, to take up more calcium than it is subsequently able to hold in solution becomes apparent, as does the ability of these substances to cause a depletion of the bones followed by precipitation in the soft tissues. Likewise the ability of vitamin D readily to cause calcifications in partially parathyroidectomized animals is explained if one remembers that the shift of calcium from the parathyroid-controlled fraction to the tissues is relatively extensive because of the almost complete dissolution of the parathyroid-controlled fraction after the temporary vitamin D stimulus has disappeared. Furthermore the ease with which pathologic calcifications may be produced in partially parathyroidectomized animals is understood if one appreciates the equilibrium-maintaining function of the parathyroid hormone in the serum. In its partial or complete absence the addition of other ions to the solution (as the introduction of phosphate) may force out precipitations of calcium, while in its presence the excess calcium ions can be taken up by the

23. Taylor, N. B., and Weld, C. B.: *Tr. Roy. Soc. Can.* **26**:13, 1932.

parathyroid-controlled fraction and thus be retained in solution until they can be eliminated by precipitation into bone or excretion.

One other point in this work remains for discussion. It relates to the cause of the lesions seen in hypervitaminosis D rather than to the cause of the calcifications. It seems clear that the mechanism of calcification is due to a shift of calcium from the blood to the tissues. On the other hand, the lesion which may conceivably be caused by the antecedent shift of calcium from the tissues to the blood is not well known. It was suggested by Ham⁴ that the withdrawal of calcium from the tissues during the upswing of the serum calcium curve in hypervitaminosis D should be considered as a possible cause of injury to the tissues. The work of McJunkin, Tweedy and Breuhaus⁹ is significant in indicating the complexities of the problem concerning the causation of damage to tissue in disturbances of calcium metabolism. They indicate the lesion to be caused, not by a direct action of calcium on the tissues, but by a disturbance of the calcium content of the cells. In this connection, it should be stated that in the experiments utilizing single doses of parathyroid hormone or vitamin D there may be two different effects produced on the tissues, one due to withdrawal of calcium and the other due to precipitation of calcium. The second follows the first quite rapidly, so that one is unable to obtain by this procedure exclusive evidence of withdrawal of calcium which has been continued for a sufficient length of time to allow pathologic lesions to mature. It is obvious, however, that the evidence points to a disturbance of calcium balance between cells and tissue fluids as a potent factor in the institution of the necrosis and infiltration by inflammatory cells. It is exceedingly interesting that in rats disturbances in the metabolism of calcium can result in the production of myocardial lesions of an inflammatory type which tend to be scattered along the smaller branches of the coronary vessels.

SUMMARY

Following a single enormous dose of activated ergosterol the serum calcium level of rats was found to rise for a period of approximately two to three days and then to fall gradually.

Pathologic calcifications did not appear in these animals when the serum calcium level was rising, but appeared in large numbers when it was falling.

As the evidence from these experiments and other sources shows that there is no direct relationship between the level of the serum calcium and the production of calcifications, it is assumed that the state of the serum calcium during the rise in its level is different from its state when the level is falling.

From the evidence at hand regarding the parathyroid hormone it seems logical to assume that the rise in the serum calcium curve is

caused by the attraction of the parathyroid-controlled fraction of the serum calcium for calcium which is obtained from the intestine, bones and other tissues.

The evidence obtained in these experiments indicates the fall in the level of the serum calcium to be caused by a release of calcium from the fraction of the serum calcium controlled by the parathyroid hormone, and as this phenomenon would necessitate the maintenance of a large amount of calcium in the serum in simple solution until it could be deposited in bone or excreted, and as the serum can retain only a small amount of calcium in simple solution, precipitation occurs in the tissues.

The toxic effect of both parathyroid hormone and vitamin D in enormous doses can be explained without assuming the portion of the serum calcium associated with the parathyroid hormone to be physiologically active.

Although the calcifications of hypervitaminosis D may be explained by a shift in calcium from the blood to the tissues, it is possible that other features of the lesions, such as necrosis and infiltration by inflammatory cells, may be caused primarily by a disturbance in the calcium balance between the cells and tissue fluids. This balance conceivably is disturbed on the upswing of the serum calcium curve because of withdrawal of calcium from the tissues. Thus the cause of the calcifications may not be identical with the cause of the necrosis and infiltration by inflammatory cells.

EXPERIMENTAL INFARCTION OF THE INTERVENTRICULAR SEPTUM OF THE CANINE HEART

AN ANATOMIC AND ELECTROCARDIOGRAPHIC STUDY, WITH A NOTE
ON THE NERVE TISSUE OF THE CONDUCTION SYSTEM

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Previous studies of experimental cardiac infarction have not dealt particularly with the changes in the interventricular septum. In man, a lesion in that location may cause grave disturbances in rhythm, sometimes total heart block and ventricular standstill. This is so both when the infarcts are recent¹ and when they have become organized into scars.² Mural thrombosis of either side of the septum, with a wide variety of sequences due to embolism, is also observed, and, while extremely rare, spontaneous perforation of the infarcted septum has been recorded.³ The exact type of disturbance depends on the location and dimensions of the infarct as well as on its age. The present study concerns the effect of infarcts produced in the interventricular septum in the dog by ligation of the septal branch of the left coronary artery.⁴ This artery was chosen because most workers agree that from it the atrioventricular node receives a large part, and the bundle of His, all, of the arterial blood supply.⁵

From the Norman Bridge Pathological Laboratory, Rush Medical College.

1. Levine, S. A., and Brown, C. L.: *Medicine* **8**:245, 1929.

2. (a) Géraudel, E., and Gautier, C.: *Ann. d'anat. path.* **8**:339, 1931. (b) Mahaim, I.: *Maladies organiques du faisceau de His-Tawara*, Paris, Masson & Cie, 1931.

3. Freeman, W., and Griffin, E. D.: *Am. Heart J.* **7**:732, 1932.

4. Throughout this paper, the term "septal artery" refers to the large branch of the left coronary artery which arises near the bifurcation of the main trunk into circumflex and anterior descending branches and penetrates the septum from in front. No attempt was made in this study to ligate the smaller, posterior branch, usually called "ramus septi fibrosi," although, as Kahn suggested in 1911, both vessels would have to be occluded to render the conduction system totally anemic.

5. (a) Haas, G.: *Anat. Hefte* **43**:627, 1911. (b) Kahn, R. H.: *Arch. f. d. ges. Physiol.* **163**:506, 1916. (c) Spalteholz, W.: *Die Arterien der Herzwand*, Leipzig, S. Hirzel, 1924. (d) Lauterbach, W.: *Ztschr. f. d. ges. exper. Med.* **61**:665, 1928. (e) Moore, R. A.: *Am. Heart J.* **5**:743, 1930.

The existence of the dog's septal artery and the difficulties attendant on its experimental occlusion have been recognized ever since the description of it in 1881 by Cohnheim and von Schulthess-Rechberg.⁶ In 1896, Porter⁷ ligated this vessel in three dogs which were not allowed to recover from the anesthetic. He was chiefly interested in the controversy then taking place over the cause of ventricular standstill after ligation of the coronary arteries, and offered his experiments as part of a demonstration that the frequency and speed of cardiac arrest were proportional to the size of the artery occluded. For ligation of the septal artery, the smallest of those tied by him, did not cause the heart to stop beating.⁸ Porter made no statement as to the condition of the septum following ligation of this artery.

Observations on the association of electrocardiographic changes with experiments on the septal artery were first reported by Kahn.⁹ He passed a ligature around the artery and noted indications of a lesion in the bundle branches, most frequently the right, when the ligature was drawn taut. More recently, the immediate changes in the electrocardiographic tracing following ligation of the septal artery in the dog were reported by Lauterbach^{5a} (1928). He produced a transitory increase in the PQ interval, followed by a partial or total block. Most typically there appeared a bundle-branch block, usually right-sided. In addition, the changes in the T wave characteristic of occlusion of a branch of the left coronary artery were noted. The experiments lasted about seven hours, and tracings were made every few minutes. Because the blood vessels in a large part of the interventricular septum were not filled with a mercuric sulphide and gelatin mixture which he injected into the coronary arteries after death, Lauterbach concluded that ischemia of the septum was the cause of the electrocardiographic changes.

For the purposes of this study, the transthoracic operative method used by Rukstinat¹⁰ was chosen, which, by avoiding rib resection and thereby subjecting the animals to as little trauma as possible, affords a means of observing the effects of interruption of the circulation to the dog's septum after the animals recover. Medium-sized mongrels

6. Cohnheim, J., and von Schulthess-Rechberg, A.: *Virchows Arch. f. path. Anat.* **85**:503, 1881.

7. Porter, W. T.: *J. Exper. Med.* **1**:46, 1896.

8. Kahn pointed out in 1916 that Porter did not make absolutely clear which of the two arteries to the septum was tied, as the designation was simply "ramus septi." Careful reading of Porter's article indicates, however, that the artery tied was in all probability the same vessel with which the present experiments are concerned.

9. Kahn, R. H.: *Arch. f. d. ges. Physiol.* **140**:627, 1911.

10. Rukstinat, G. L.: *J. A. M. A.* **96**:26, 1931.

of even disposition were used. The operations were performed under ether anesthesia, with sterile precautions; the manner of preparation and ligation of the septal artery did not differ essentially from that described by previous observers.¹¹ The dogs died or were killed at intervals of from twenty minutes to three months after ligation of the artery. Death was brought about in the majority of the animals by high section of the spinal cord. In this way, the dogs died practically instantaneously, and it was usually possible to avoid the agonal changes, such as sub-endocardial hemorrhage, that accompany death from an overdose of ether. Observations of the rhythm of the heart beat were made by palpation and auscultation, and, when possible, with the electrocardiograph. After death, the brain and the organs of the chest and abdomen were examined.

The operation is difficult, and a number of dogs died of hemorrhage while still anesthetized. In others surviving, the ligature had not been placed about the artery, and infarction of the intraventricular septum had not occurred. However, in twelve dogs, conditions were obtained suitable for study; i. e., the septal artery had been occluded either wholly or in part, and infarction of the interventricular septum of greater or less degree had followed.

Classified according to the degree of occlusion of the septal artery, the twelve experiments fell naturally into four groups (table).

Unique among the experiments was that on dog 1, which constitutes the first group. Ligation of the septal artery was followed by marked dilatation and cyanosis of the heart, which stopped beating twenty minutes after the ligature had been tied. Only microscopic changes were found in the septum. These consisted chiefly in an engorgement of the veins with blood. It is not possible to decide with certainty just how much influence the cutting off of the blood supply to the septum had in producing death, for two other dogs died on the operating table with the same signs of cyanosis and cardiac dilatation, without any ligation having taken place, and in one of them there was difficulty with the artificial respiration.

Six experiments¹² in which the septal artery was completely occluded by the ligature, and in which the lesion that came to be recognized as a typical infarct was produced, form group 2 (dogs 2 to 7 inclusive, in the table). The infarct was always extensive on the left ventricular surface of the septum, occupying from one fourth to three fourths of that surface. The changed region extended from the attached margins

11. Kahn.^{5b} Lauterbach.^{5d} Kahn.⁹

12. The first four of these were reported briefly in a preliminary statement read at the meeting of the Illinois section of the Society for Experimental Biology and Medicine in February, 1932 (*Proc. Soc. Exper. Biol. & Med.* **30**:15, 1932).

Summary of Experiments

Experi- ments	Dog	Time Between Operation and Death	Condition of Septal Artery	Change in Septum	Approximate Fraction of Auriculoventricular Node Infarcted	Postoperative Electrocardio- graphic Notes	Complications	Mode of Death
Group 1	1	20 min.	Occluded by ligature	Veins engorged with blood	Undetermined	No tracings	Cardiac dilatation ending in death	Spontaneous
Group 2	2	66 days	Occluded by ligature	Infarct	Undetermined	No tracings	None	Ether
	3	11 days	Occluded by ligature	Infarct	One seventh	Regular sinus rhythm	Emaciation; bron- chopneumonia	Spontaneous
	4	5 days	Occluded by ligature	Infarct	Undetermined	No tracings	Suppuration of wound	Spontaneous
	5	6 days	Occluded by ligature	Infarct	One third	Tachycardia; reg- ular sinus rhythm	Suppuration of wound	High section of spinal cord
	6	7 days	Occluded by ligature	Infarct	One half	Tachycardia; transient complete heart block	Suppuration of wound	High section of spinal cord
	7	42 days	Double; one branch occluded by ligature	Infarct	No change	Tachycardia; extrasystoles	Suppuration of wound; pyopneumo- thorax; recovery	High section of spinal cord
Group 3	8	52 days	Narrowed by ligature	Microscopic hemorrhage and necrosis	Undetermined	Regular sinus rhythm	Distemper; recov- ery; emaciation	High section of spinal cord
	9	90 days	Almost com- pletely occluded by ligature	Infarct	One twentieth	Tachycardia; reg- ular sinus rhythm	None	High section of spinal cord
	10	3 days	Not included in knot; narrowed from without	Small, atypical infarct	One tenth	Regular sinus rhythm	Suppuration of wound	High section of spinal cord
Group 4	11	5 or 6 days	Surrounded by ligature but patent	Microscopic necrosis	No change	Regular sinus rhythm	Suppuration of wound	Spontaneous
	12	3 days	Patent	Infarct	No change	Regular sinus rhythm	Suppuration of wound; infarct of outer wall of left ventricle	Spontaneous

of the aortic cusps toward the apex of the left ventricle. The widest portion of the infarct was usually a short distance below the aortic ring. The edges were well defined and jagged (figs. 1 and 2*A*).

In two hearts (dogs 6 and 7) both surfaces of the septum were correspondingly altered (fig. 2*B*); in two others (dogs 2 and 4) the gross change on the right side of the septum was slight; in the remaining two of this group there was no noteworthy gross alteration of the surface of the right side of the septum.

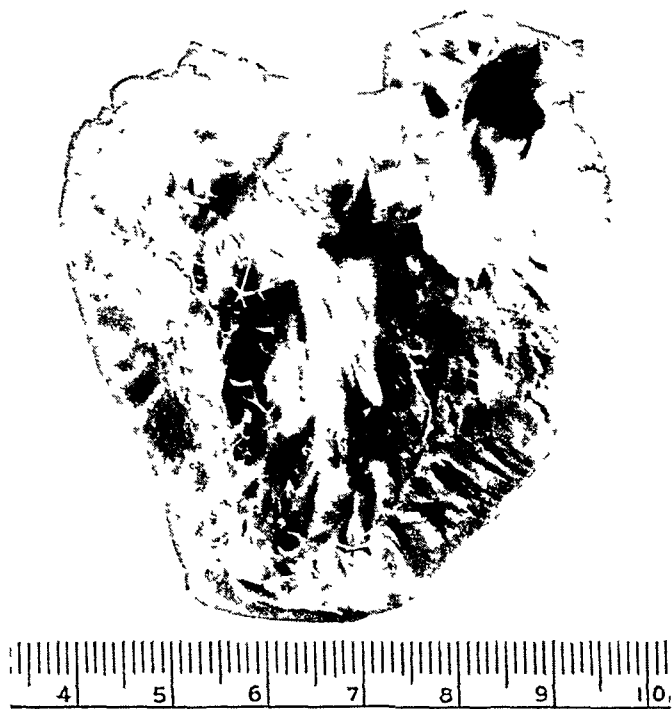


Fig. 1 (dog 2).—The infarcted left side of the interventricular septum is shown. The lesion extends from the aortic ring toward the apex of the heart and is typical of the position of the infarcts caused by ligation of the septal artery. The specimen was fixed in Kaiserling's solution.

In all six hearts, the endocardium was intact on both sides of the septum; indeed, the bands of Purkinje's fibers, gray against the darker infarcted muscle beneath them, were vivid and easily followed because the endocardium was so normally translucent.

Microscopically, the alterations in the interventricular septum were chiefly confined to the muscle. The stages of infarction varied from the acute changes in the hearts of dogs 4, 5 and 6, which had lived less than a week after the operation, to the later stages of organization and repair present in dog 3 (eleven days) and in dog 7 (fifty-nine days). The protocols should be consulted for details of these lesions. Suffice

it to say here that the alterations were usually consistent with the gross appearance.

In the third group of experiments (dogs 8, 9 and 10), the channels of the septal arteries were found incompletely obliterated at the site of ligation, and the infarcts in two of the septums were small and not in the usual location. The lesion of dog 9, however, was in all particulars like the lesions in the dogs of group 2. Since the septal arteries of dogs

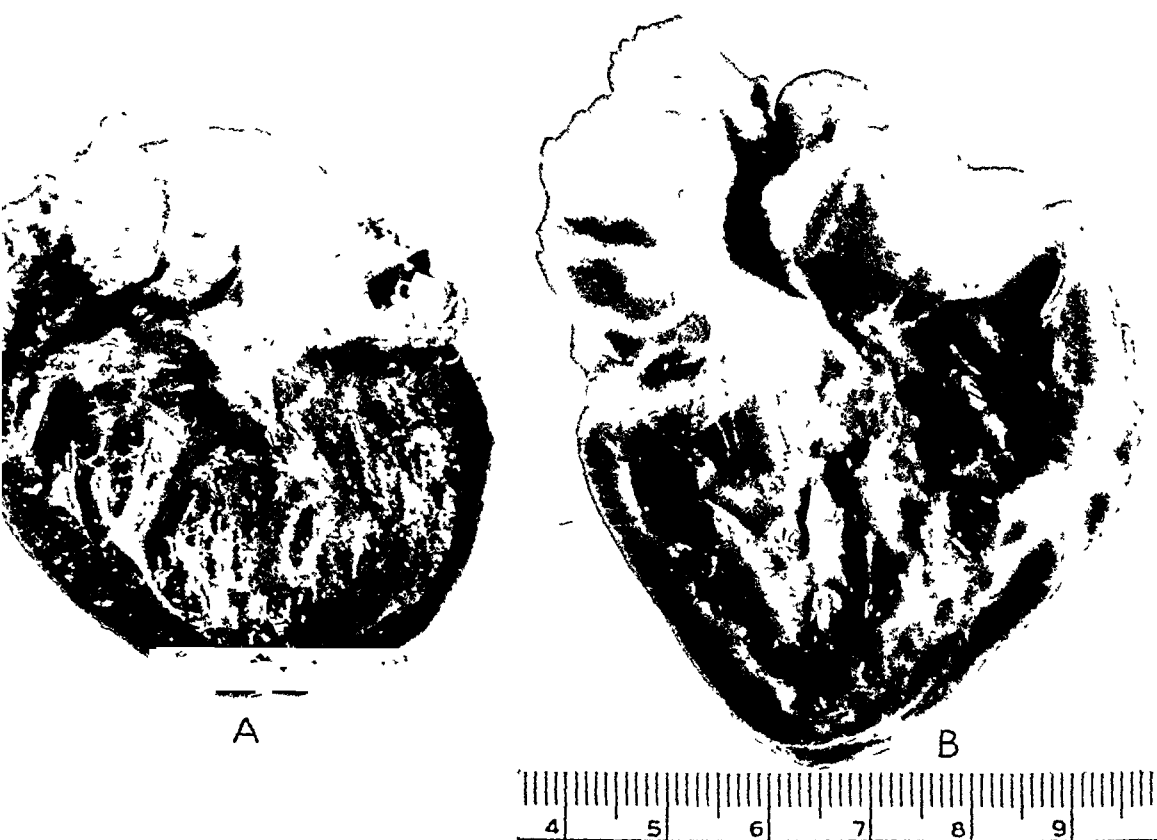


Fig. 2 (dogs 3 and 7).—*A*, the heart of dog 3; unfixed specimen. The photograph was taken on a slant; hence the gray region of infarction below the aortic cusps appears relatively smaller than it actually was. The electrocardiogram of this dog is pictured in figure 5 *A*. *B*, the right side of the septum of dog 7; unfixed specimen. The lesion is to the right of the reflected tricuspid leaflet and involves the base of the papillary muscles. In the changed region, the septal wall is noticeably thinned. For the corresponding electrocardiograms see figure 6.

8 and 9 were completely surrounded by the ligating thread when examined after death, it is possible either that the arteries were incompletely occluded at the time of operation, or that recanalization took place subsequently. The acute inflammatory reaction about the operative field

probably accounts for the narrowing of the septal artery of dog 10, for the ligature did not surround the artery.

In the fourth group are two experiments (dogs 11 and 12) in which the septal arteries were patent at the time of the postmortem examination. The changes in the septum of dog 11 were microscopic, but the lesion in dog 12 was extensive and involved the outer wall of the left ventricle as well as the septum. In both dogs, inflammation in the wound, in addition to the trauma of the operative manipulations, must have caused temporary occlusion of the septal artery, of sufficient duration to produce the lesions.

NERVE TISSUE IN THE CONDUCTION SYSTEM

In the microscopic examination of the conduction systems of these dogs, a special study was made of the nerves and ganglion cells associated with the specialized muscle tissue.

The anatomic relations of the ganglion cells in the conduction system have been described by so few observers¹³ that a preliminary study was made to establish the normal conditions. Six hearts were removed from apparently normal and lively dogs after the animals had been killed by an overdose of ether. The right and left ventricular and auricular walls of the lateral sides were cut away, leaving only the interventricular and interauricular septum. The block containing the structures pertinent to this study was removed by making four cuts along the following lines: one, in the vertical axis of the heart 4 mm. anterior to the coronary sinus; a second, parallel to the first, through the middle of the anterior tricuspid leaflet; a third, parallel with the tricuspid ring and 2 mm. below it, and a fourth, parallel with the third, 1 cm. above the ring. This block was sliced into sections from 1 to 2 mm. thick by cuts parallel to the long axis of the heart, and these sections were stained with intravital methylene blue according to a modification of the immersion technic of Wilson.¹⁴

Microscopic sections were cut to about 10 microns. In addition, a number of sections from each heart were destained of methylene blue by creosote and restained with hematoxylin and eosin.

The conditions were essentially the same in all the hearts. Numerous nerve trunks, taking a deep blue stain and readily differentiated from

13. Wilson, J. G.: *Proc. Roy. Soc., London* **81**:151, 1909. DeWitt, L.: *Anat. Rec.* **3**:475, 1909.

14. This method differed from that of Wilson in that absolute instead of 95 per cent alcohol was used for dehydration, and that embedding was in a concentrated preparation of pyroxylin (celloidin) instead of paraffin. It was found early in the work that the dye was leached from the tissues by the more dilute alcohol, even after they had been embedded in the pyroxylin.

connective tissue bundles by the nodules of the nerve fibers, were found throughout the region from the coronary sinus to the commissure of the medial and anterior tricuspid leaflets and from the auriculoventricular fibrous septum to about 1 cm. above the tricuspid ring. The nerves varied from fine fibrils to very coarse trunks and differed greatly in the intensity with which they took the methylene blue. Small nerve fibers were found entering muscle cells. Throughout the region occupied by nerves were numerous separate ganglion cells and many ganglion cell groups, lying in the adipose tissue between the specialized muscle cells. The number of ganglion cells in each group varied from five to more than one hundred. The largest groups of ganglion cells lay about the middle of the block or about from 1 to 1.5 cm. from the coronary sinus and 0.5 cm. above the fibrous auriculoventricular septum. Some of the groups lay along large trunks (fig. 3*A*), while nerve trunks led from others. There were a few individual ganglion cells along the course of the nerve trunks; others were isolated. Toward the lower end of the atrioventricular node the ganglion cell groups diminished in size and number. The majority of the ganglion cells were multipolar (fig. 3*B*), and each was surrounded by a thin endothelial capsule. The nucleus was large and round or oval, and stained deeply with methylene blue. However, in every group there were a few ganglion cells which did not stain with methylene blue.

In sections stained with hematoxylin and eosin, the ganglion cells were not so pronounced as in those stained with methylene blue, but the nuclei were deep purple, and the cytoplasm was light pink. The cell processes were visible but indistinct. The capsules about the ganglion cells were formed of long, thin, flat cells.

The same method being used, one human heart was examined, which was obtained six hours after the death of a patient from bullet wounds. One group of five ganglion cells was found about 1 cm. from the coronary sinus and about 0.5 cm. above the auriculoventricular fibrous septum. The cells were similar to those found in the dog's heart, except that they were slightly smaller. In addition to the group, several discrete ganglion cells were scattered throughout the node. Nerve trunks were numerous and similar in all respects to those in the dog's heart.

Heretofore observers have dealt mainly with the conduction systems of animals others than dogs and man, in regard to the nerve tissue there, although it has been studied in both species. The reports lead one to believe that ganglion cells, nerves and nerve trunks are scarce in the hearts of these animals. The results of the foregoing studies indicate that the contrary is the case. The matter resolves itself into one of patient and diligent searching, from which it must be conceded

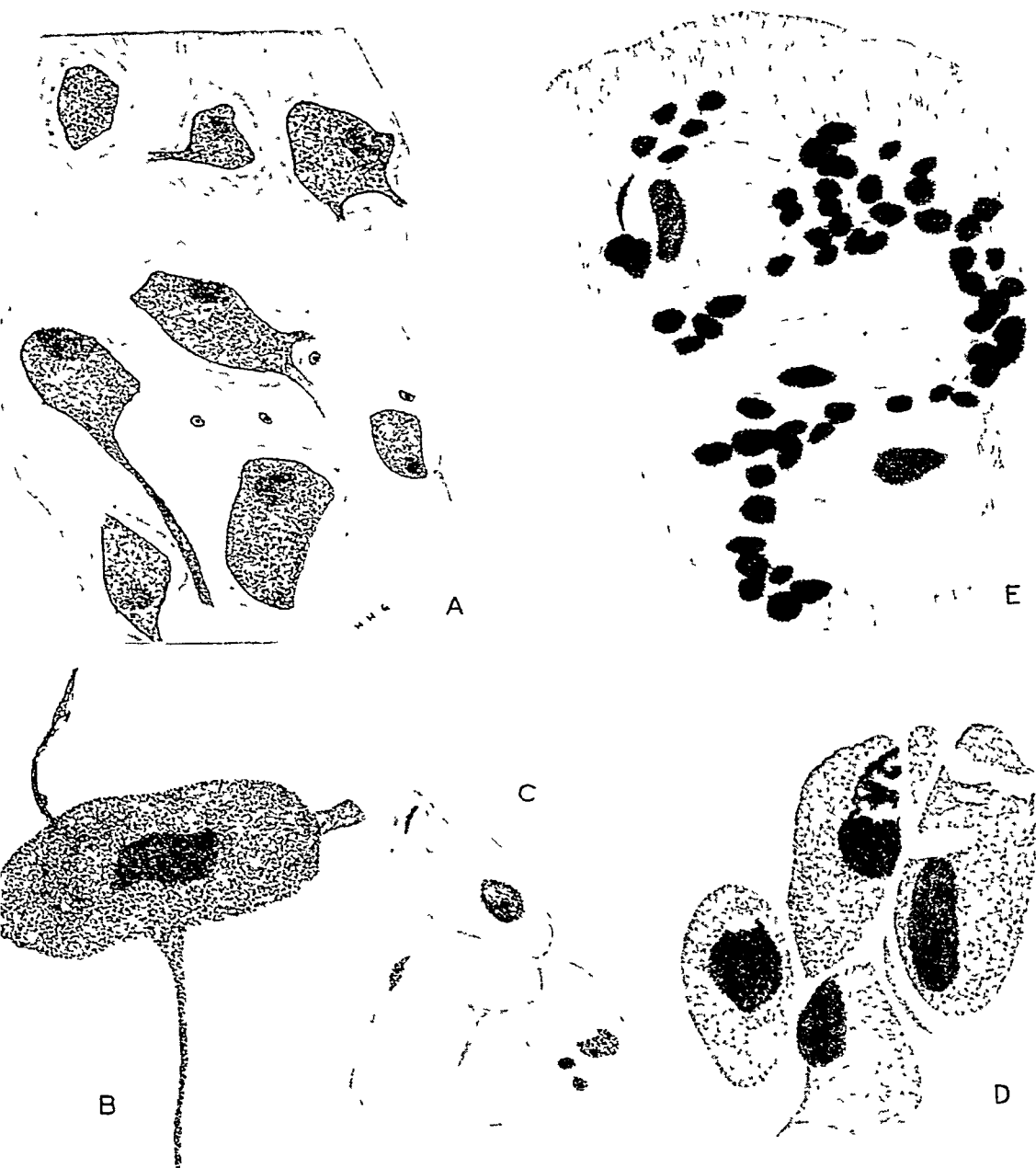


FIG. 3.—*A*, ganglion cell group in the auriculoventricular node of a normal dog; intravital methylene blue. The group is traversed by a nerve trunk. *B*, a typical multipolar ganglion cell in the auriculoventricular node of a normal dog; intravital methylene blue. *C*, part of a ganglion cell group in the auriculoventricular node of a dog following infarction of the interventricular septum; hematoxylin and eosin. Note the absence of some ganglion cells from their endothelial capsules and the fragmentation of one cell. *D*, fragmentation of ganglion cells in part of a group in the auriculoventricular node of a dog following infarction of the interventricular septum; intravital methylene blue. *E*, portion of a ganglion cell group infiltrated by leukocytes following extensive infarction of the interventricular septum; intravital methylene blue. The cytoplasm of the leukocytes is practically indistinguishable. See the protocol of dog 6 and the electrocardiograms in figure 4.

that nerves, nerve trunks and ganglion cells are prominent in the dog's conduction system and less so in that of man.

For demonstrating nerves and ganglion cells, the same method that had been used in the work on normal dogs' hearts was then applied to the hearts of eight animals in which ligation of the septal branch of the left coronary artery had brought about infarction of the interventricular septum. In five of the eight infarcted hearts, the ganglion cells of the conduction system were unaltered, in two slightly altered, and in one markedly so. The changes were essentially of the same type, differing only in degree. Many ganglion cells were absent from their endothelial capsules (fig. 3C). Others failed to stain with methylene blue, although they could be distinguished because of a network of nuclear material. In one heart the nuclei were pyknotic, there was fragmentation with extrusion of the nuclei (fig. 3D), and infiltration by leukocytes was seen in some of the ganglion cell groups (fig. 3E).

It was considerably more difficult to find ganglion cells in the three hearts in which they had been altered than in the other hearts. This was true whether the sections were stained with methylene blue or with hematoxylin and eosin.

Sections of the atrioventricular nodes of nine dogs were stained with hematoxylin and eosin. In four (dogs 7, 8, 11 and 12), the nodal tissue was unchanged. The fraction of changed tissue in other nodes was approximately as follows: dog 9, one twentieth; dog 10, one tenth; dog 3, one seventh; dog 5, one third; dog 6, one half. There was no close parallel between the changes in the nodes recognized as infarcts and the changes found in ganglion cells.

ELECTROCARDIOGRAMS

Electrocardiograms were used in this study for the purpose of demonstrating changes in the cardiac rhythm that might conceivably be the sequence of ligation of the septal artery. As noted, such changes occurred in the acute experiments of Lauterbach.^{5d} The results of the present experiments in this regard are summarized in the table.

Electrocardiograms were not made for dogs 1, 2 and 4. Tracings for dogs 3 and 6 were made only after operation. The records of all the other dogs include electrocardiograms made before operation as well. The shortest interval between operation and tracing was nine hours; the longest, twenty days. When feasible, a final tracing was made as near the time of postmortem examination as possible. All tracings were made with the dogs in the dorsal position and without anesthesia or sedatives of any kind. Dr. C. J. Lundy contributed much assistance and counsel in recording and interpreting the electrocardiograms.

There was a striking similarity in the changes in the electrocardiograms following operation in two particulars. First, the immediate effect on the rate was an increase often up to double that present in tracings made before ligation. Second, the changes, with one exception, had little or no relation to heart block. The one exception was the first postoperative tracing for dog 6 (fig. 4), made twenty-four hours after operation. In it the auricular waves were completely dissociated from the ventricular complexes. Subsequently, the normal relationships were resumed.

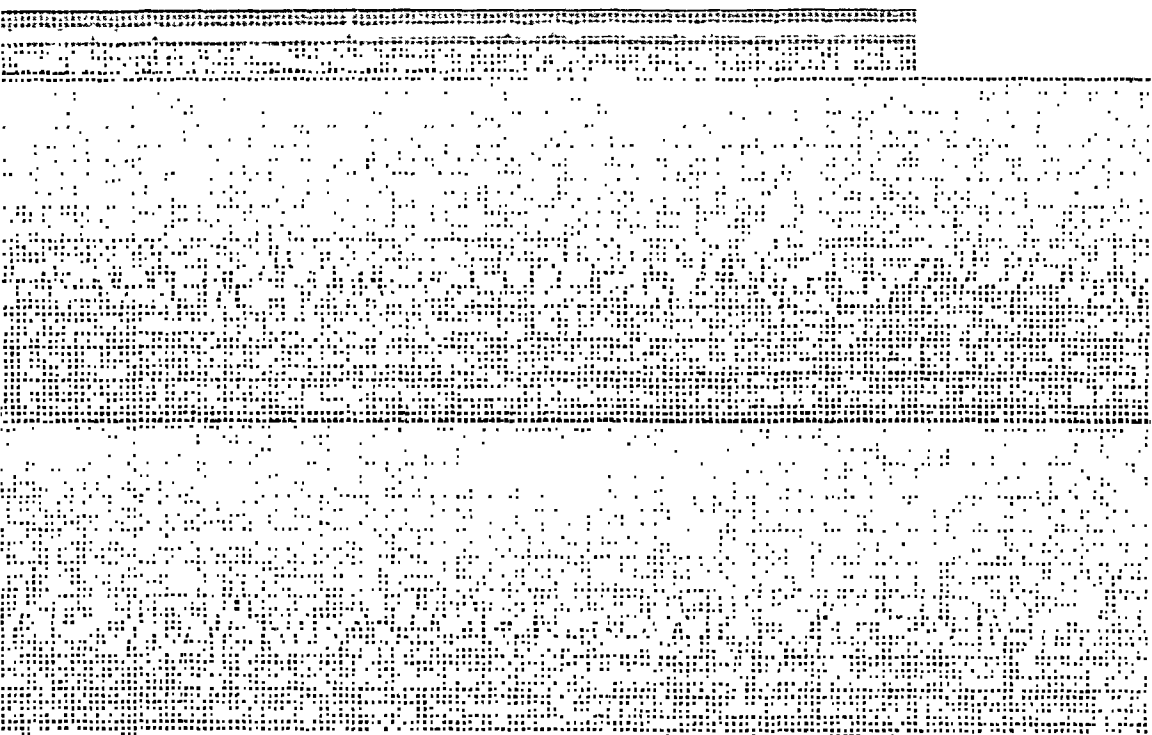


Fig. 4 (dog 6).—Electrocardiogram taken twenty-four hours after operation. It records complete auriculoventricular dissociation; auricular rate, 176; ventricular rate, 200; QRS, from 0.05 to 0.10 second. There is shown a combination of complete heart block, auricular and ventricular tachycardia and many ventricular extrasystoles.

A frequent alteration noted in the configuration of the T wave is that seen in the tracings for dogs 6, 7 and 9 (figs. 5 *D* and *F* and 6 *C*), a change considered by some authorities characteristic of occlusion of a branch of the left coronary artery.¹⁵

In correlating the anatomic changes in these experiments with the electrocardiograms, one is impressed with the fact that, although the artery presumably carrying the major portion of the blood supply to

15. Pardee, H. E. B.: *Am. J. M. Sc.* **169**:270, 1925.

the conduction system was occluded sufficiently to cause infarction of a large portion of the septum between the ventricles, lasting heart block of any sort did not result. The most profoundly altered electrocardiogram, the only tracing in which there was demonstrated for a while at least complete heart block, was that for the dog in which the septum and auriculoventricular node showed the greatest amount of change (dog 6, fig. 4). Perhaps if tracings had been made sooner after operation than was usual in this study, heart block, even though transient, might have been recorded more frequently. But the bizarre tracing for dog 7, made nine hours after ligation of the septal artery, illustrates that this is not necessarily the case. In it there are shown marked tachy-

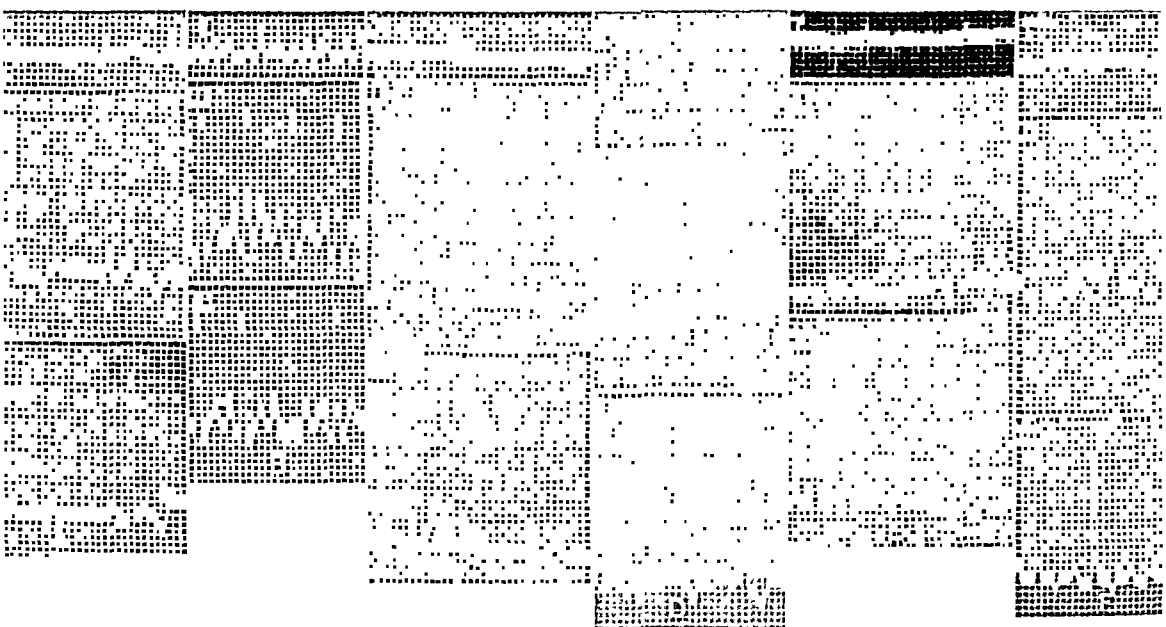


Fig. 5 (dogs 3, 5, 6 and 9).—*A*, electrocardiogram of dog 3 ten days after operation: cardiac rate, 75; PR, 0.12 second; QRS, 0.06 second; $T_{2,3}$, inverted. No evidence of auriculoventricular dissociation. *B*, electrocardiogram of dog 5 five days after operation: cardiac rate, 214; regular sinus rhythm; PR, 0.10 second; QRS, 0.06 second. The rate is more than double that recorded before operation, while the PR interval is the same. This suggests a possible delay in auriculoventricular conduction, but cannot be accepted as good evidence. *C*, electrocardiogram of dog 9 before operation: cardiac rate, 83; sinus arrhythmia; PR, from 0.12 to 0.16 second; QRS, 0.06. Note height of $T_{2,3}$. *D*, electrocardiogram of dog 9 five days after operation: cardiac rate, 145; regular sinus rhythm; PR, 0.10 second; QRS, 0.06 second; ST_1 , markedly elevated; ST_3 , depressed; T_3 , inverted. *E*, electrocardiogram of dog 6 before operation: cardiac rate, 93; sinus arrhythmia; PR, 0.12 second; QRS, 0.05 second; somatic tremor. *F*, electrocardiogram of dog 6 four days after operation: cardiac rate, 170; occasional ventricular extrasystole; PR, 0.14 second; QRS, 0.06 second; $ST_{1,2,3}$, elevated; $T_{2,3}$, inverted. The smallest vertical divisions of the graphs represent 0.04 second. White dots indicate the limit of excursion.

cardia and a profusion of extrasystoles, but no sign of atrioventricular dissociation¹⁶ (fig. 6B).

There seemed to be nothing in the alterations of most of the tracings which could be considered a specific indication of the presence of the septal infarct. It was not possible to predict correctly the presence or the absence of an infarcted septum by examining the electrocardiograms, with the one exception (dog 6) noted in a foregoing paragraph, in which complete dissociation was so striking.

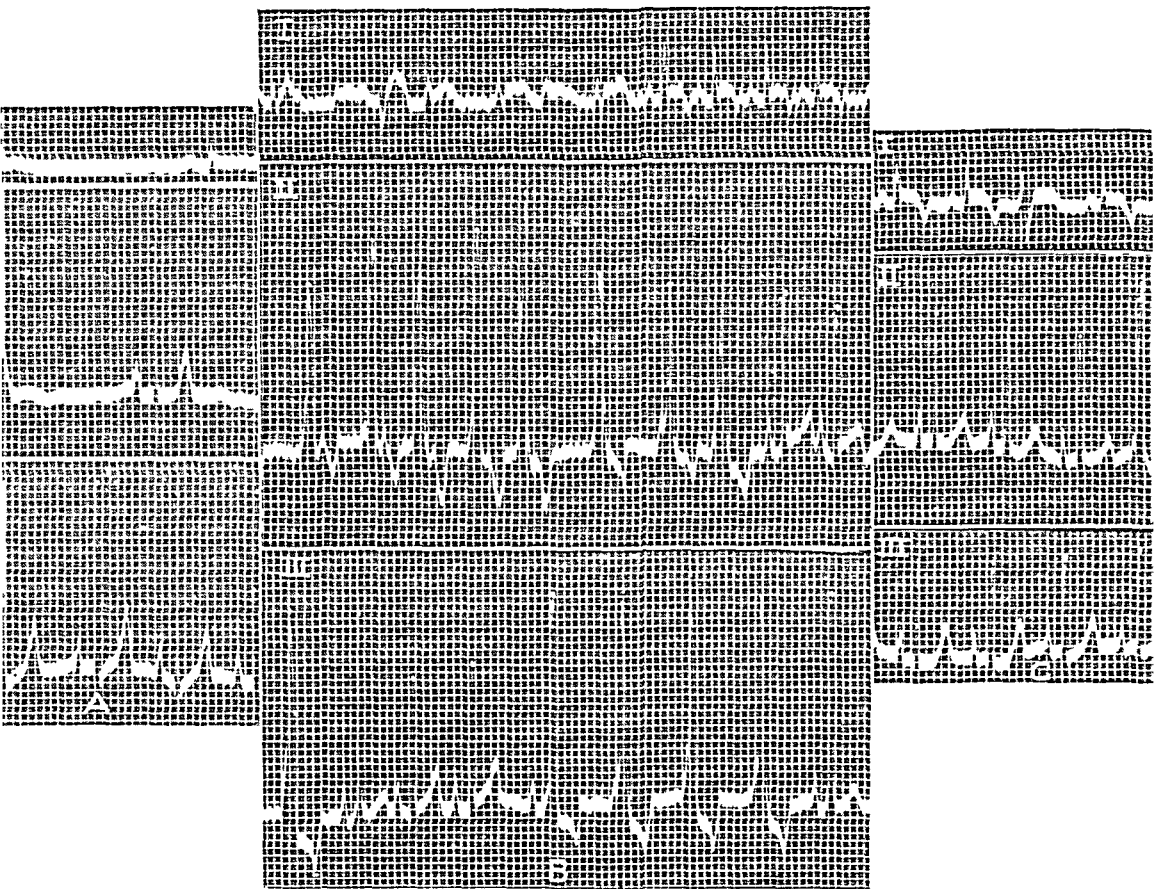


Fig. 6 (dog 7).—*A*, electrocardiogram taken before operation: cardiac rate, 80; sinus arrhythmia; PR, from 0.08 to 0.10 second; QRS, 0.04 second. Note height of $T_{2,3}$. *B*, electrocardiogram taken nine hours after operation: cardiac rate, 190; PR, 0.08 second; QRS, 0.04 second; many ventricular extrasystoles, no heart block. *C*, electrocardiogram taken twenty-four hours after operation: cardiac rate, 170; PR, 0.09 second; QRS, 0.04 second; ST_1 , elevated; T_1 , inverted; occasional extrasystoles.

Neither was there a constant relationship between the electrocardiographic changes and the alterations in the ganglion cells of the conduction

16. Post mortem, the septal artery was found to be double, only one of the branches having been occluded.

system. True, the ganglion cells of dog 6 suffered the most damage of all, and the animal had a transient heart block. If one assumes that the ischemia produced retrogressive changes in the node from which the sensitive ganglion cells were unable to recover, whereas similar changes were slight or reversible in enough of the hardier Purkinje fibers to allow conduction eventually to proceed, one is tempted to infer that the ganglion cells are, therefore, not primarily concerned with the mechanism of the conduction of the cardiac impulse.

The reversible nature of the phenomenon of block has been emphasized by Kisch¹⁷ in his experiments on the action of perfused isolated canine hearts. Before perfusing the heart, he had clamped off the left coronary artery at its origin in order to shut off the circulation to the conduction system from both front and rear septal arteries. When perfusion was well under way, with the auricles beating from thirty to fifty-five times and the ventricles once per minute, the obstruction was removed from the left coronary artery, and the right coronary artery was clamped. The auricular and ventricular beats then assumed their normal relationship to each other. Release of the right coronary artery and reclamping of the left then produced a gradually increasing interference in conduction which, within four minutes, resulted in complete auriculoventricular dissociation.

It is probable that in the experiments of Lauterbach,^{5d} which have been referred to, the heart block produced was of the same transitory nature as in our experiments, and would have disappeared with the passage of time had his dogs lived.

That tachycardia frequently follows coronary occlusion, both experimental and otherwise, is well known, but as far as we are aware, previous observers have not paid particular attention to the effects of infarcts produced by interruption of the circulation to the conduction system specifically. It would seem that the results of the infarcts produced in the present experiments point to the irritative type of lesion recently stressed by Mahaim.^{2b} Hyperexcitability was evidenced by the tachycardia and premature contractions. The reason more frequent or more permanent heart block did not occur is probably that the circulation of blood to the septum from behind was usually adequate to prevent interruption of the continuity of the His-Tawara system.

PROTOCOLS

Dog 1.—After ligation of the septal artery, the heart became cyanotic, dilated, and stopped beating while the chest was being closed, twenty minutes after the artery had been tied. The ligature was found tight around the septal artery. There was no noteworthy gross alteration of the myocardium. Microscopically, the small veins were engorged with blood.

17. Kisch, B.: *Deutsches Arch. f. klin. Med.* **135**:281, 1921.

DOG 2.—Recovery from the operation was uneventful. The heart beat was regular, the rate on one occasion being 120 per minute. Six weeks after operation, as the dog had become emaciated and weak, and refused food, it was killed by an overdose of ether. The septal artery was found occluded, and there was an infarct in the interventricular septum occupying four fifths of the left and less than one tenth of the right side, composed largely of fibrous tissue (fig. 1).

DOG 3.—Following the operation, the dog recovered well, and there was no cardiac irregularity. On the tenth day, it became weak and refused food, and tremors of the extremities developed. An electrocardiogram was made in which there was no sign of auriculoventricular dissociation (fig. 5 *A*). The following day, the eleventh since the ligation of the septal artery, the animal died spontaneously.

There was an infarct, already partly organized into fibrous tissue, occupying one fourth of the left side of the interventricular septum (fig. 2 *A*). Microscopically, about one seventh of the Purkinje tissue of the auriculoventricular node was similarly altered.

Death was apparently due to bronchopneumonia, evidence of which was abundant in both lungs.

DOG 4.—During the operation, the fifth rib was accidentally fractured. The postoperative course was stormy owing to infection in the wound, and the dog died on the fifth day without evidence of cardiac irregularity. No electrocardiogram was made.

The infarct in the interventricular septum was a spatula-shaped region of friable, yellow tissue occupying the middle of the left surface and a smaller portion of the right. On the left side, the upper margin of the lesion was at the aortic ring. The microscopic changes were those of coagulation necrosis, hemorrhage and leukocytic infiltration.

The left lung had been pierced by the rough end of the broken rib, and there was a fibrinopurulent exudate in the left pleural cavity and the pericardial sac.

DOG 5.—The heart rate as recorded by electrocardiogram before operation was 100 per minute. Immediately following ligation of the septal artery, the heart dilated so that it was impossible to close the pericardial sac. Three days later the pulse was 160 per minute and regular. In an electrocardiogram taken on the sixth day, the rate was recorded as 214 per minute and the rhythm was shown to be regular (fig. 5 *B*). Because of suppuration of the wound, the dog was then killed by high section of the spinal cord under anesthesia.

There were two arteries of unequal size at the usual location of the septal artery. Only the larger was occluded by the ligature. The infarct occupied one third of the left side of the septum. Over the infarcted muscle the left branch of the bundle of His was plainly visible through the smooth, transparent endocardium. Microscopically, about one third of the auriculoventricular node was infarcted.

DOG 6.—Although the anesthesia was not excessively deep, the heart dilated during the preliminary dissection of the coronary arteries, and the left ventricle stopped beating. The region of the sino-auricular node was massaged briefly, and the heart again beat naturally. The septal artery was ligated without further event. The first electrocardiogram was made twenty-four hours later. In it there was demonstrated complete atrioventricular dissociation (fig. 4). During the next six days, two tracings were made in which there was no indication of block (fig. 5 *F*). Because of infection in the wound, the dog was killed by high section of the spinal cord seven days after operation.

There were left fibrinopurulent pleuritis and mediastinitis. A large infarct involved three fourths of the left side of the interventricular septum and an equal amount of the right side. The endocardium was shiny and transparent. The course of the branches of the bundle of His was faint. The entire thickness of the septum was infarcted. Microscopically, about one half of the auriculoventricular node had been similarly changed, and the ganglion cells in it were altered by marked retrogressive changes and leukocytic infiltration (fig. 3 E).

Dog 7.—There was nothing unusual of importance noted during the ligation of the septal artery. An electrocardiogram made nine hours later recorded many extrasystoles, and the cardiac rate was more than double that before operation (fig. 6 A and B). In subsequent tracings made twenty-four and forty-five hours after ligation, the premature contractions diminished in number and then disappeared, but the rate remained rapid (fig. 6 C). During the first week, there was some drainage from the incision, but otherwise the wound healed well, and the dog lived uneventfully with a normal cardiac rate and rhythm till the fifty-ninth day after operation, when death was produced by high section of the spinal cord under ether anesthesia.

The septum was thinned in a region of old infarction 3 by 1 cm. involving from one fourth to one third of its muscle (fig. 2 B). The septal artery was double; one branch only had been ligated. Microscopically, the septal infarct contained fibrous tissue; no change was found in the Purkinje fibers of the auriculoventricular node.

Dog 8.—During the first week after operation, the dog evinced weakness, lassitude and loss of appetite and had a caking discharge from the nose and eyes. However, it recovered from this distemper and again became vigorous. Electrocardiograms were made twenty and fifty-one days after operation. There was no alteration in the rate or rhythm of the heart. Six or seven weeks after operation, the dog lost its appetite, and tremors, spasticity of the extremities and extreme weakness gradually developed. It was killed on the fifty-second day by high section of the spinal cord under ether anesthesia. The diaphragm continued to contract and the heart to beat after the limbs were flaccid. The cardiac contractions were regular and appeared normal.

The ligature was found to surround the septal artery completely; the arterial channel had been narrowed so as to admit only a fine broom-straw. There was no infarct visible grossly in the septum, but there was histologic evidence of diffuse scarring and fresh hemorrhage. There were extensive fatty changes in the liver. The lungs and brain were not remarkable.

Dog 9.—The first postoperative electrocardiogram was made on the fifth day. The rate was almost double; there was no heart block (fig. 5 C and D). During the next eleven weeks, the dog's condition was good. Electrocardiograms were made seven and twelve weeks after operation. In the first of these, one ventricular extrasystole was recorded. The animal was killed three months after operation by high section of the spinal cord under ether anesthesia.

The infarct in the septum was a depressed, spatulate, fibrous scar extending from the aortic ring to within 1 cm. of the apex of the left ventricle. It occupied one third of the left surface of the septum and extended into the muscle one fourth of the width of the septal wall. The septal artery was narrowed by the ligature to a channel which allowed the passage of a coarse bristle. Distal to the annulation, the lumen of the artery was of normal width and the lining unaltered. Microscopically, about one twentieth of the auriculoventricular node was scarred.

Dog 10.—The septal artery was not seen during the operation; the ligation was made blindly. Because of infection in the wound, the dog was killed, while anesthetized, the third day after operation. The chief changes recorded in an electrocardiogram made just before death were tachycardia and an elevated ST interval.

There were extensive left serofibrinous pleuritis and pericarditis. The septal artery was not included in the silk knot, which lay close by, to the right of the left anterior descending branch. The channel of the septal artery, however, 3 mm. from its mouth was narrowed to a diameter of less than 1 mm. On the left side of the septum, there were four well defined infarcts, the largest, 10 by 13 mm. and extending through the septal wall. Both right and left branches of the bundle of His were plainly visible under the transparent endocardium. In the outer wall of the left ventricle, near the site of operation, the muscle was dead in a region 7 by 5 mm. Microscopically, in the infarcted regions, there were coagulation necrosis, hemorrhage and leukocytic infiltration. About one tenth of the auriculo-ventricular node was infarcted.

Dog 11.—The heart beat regularly and rapidly on the day following the operation. On the fourth day, the rate recorded by electrocardiogram was 136 per minute. There was no noteworthy change of the rhythm. The incision was intact, and the dog appeared in good condition. On the sixth day, it was found dead.

There was an abundant fibrinopurulent exudate in the left pleural cavity compressing the left lung. In the right pleural cavity was about 50 cc. of cloudy, watery liquid. The right lung was soggy with dark red blood; the liver also was bloody. Fibrin joined the visceral to the parietal pericardium about the operative field. The septal artery was completely surrounded by the silk ligature, but its lumen was uncompromised. No gross change was observed in the inter-ventricular septum. In histologic sections of the middle of the septum, there were scattered regions of necrosis and hemorrhage. There was no change in the auriculo-ventricular node.

Dog 12.—The septal artery was not seen during the operation; the ligation was attempted by passing the thread blindly under the trunk of the left coronary artery near its bifurcation into descending and circumflex branches. Twenty-eight hours after the operation, the rate as recorded by electrocardiogram was 115 per minute, the rhythm regular. On the fourth day, the dog was found dead.

There were left fibrinous pleuritis and pericarditis. The septal artery was unobstructed; its exact relation to the silk knot could not be determined. Grossly, the septal infarct was a well defined truncated cone, reaching from the aortic cusps 2.7 cm. toward the apex of the left ventricle, and extending half way through the wall of the inter-ventricular septum. The bases of both papillary muscles were infarcted, and there was an infarct a few millimeters square near the base of the tricuspid leaflets. The most conspicuous histologic changes were fragmentation of the muscle fibers and hemorrhage between the muscle bundles. There was no change in the auriculoventricular node. Passive hyperemia of the lungs, liver and kidneys was marked.

SUMMARY AND CONCLUSION

Nerve trunks, nerve fibers, groups of ganglion cells and individual ganglion cells are abundant throughout the auriculoventricular node of the dog's heart, and are present to a less degree in the node of man.

When the front septal branch of the left coronary artery of the dog was occluded by ligation and when the animals had recovered from the

immediate effects of the operation, a typical infarct was produced in the interventricular septum, and usually in part of the auriculoventricular node as well. Some of the ganglion cells and ganglion cell groups in such infarcted nodes had undergone degenerative changes.

No permanent interruption of conduction as a result of these lesions was discoverable by electrocardiograms. Mural thrombosis of the cavities of the heart was not observed. Among the possible reasons for the paucity of conduction disturbances are the richness and the variability in the arterial blood supply to the conduction system of the dog and the frequency with which the endocardium and the Purkinje fibers over the infarcts were found intact.

RELATIONSHIP BETWEEN TRAUMA SUSTAINED AT BIRTH AND ENCEPHALITIS IN CHILDREN

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In the experience of most pathologists there appear from time to time cases of encephalitis in children which are not associated with acute general infections or well established forms of encephalitis and for which the etiology remains obscure. In the literature the cases are classified as encephalitis of idiopathic origin (Brain, Hunter and Turnbull,¹ Stooss,² Kemkes and Saenger,³ Low,⁴ Citron, Seidmann and Zappert,⁵ Eckstein⁶), as atypical forms of encephalitis (Wilckens,⁷ Stern,⁸ Weimann,⁹ Eckstein,⁶ Citron, Seidmann and Zappert⁵), as insidious encephalitis (Guillain¹⁰) and as encephalitis following pyogenic infections (Grinker and Stone¹¹). In many of these cases the location of the lesion, the fatty changes and the cortical atrophy usually associated with paralysis cannot be wholly explained by the infection (Spielmeyer,¹² Stern⁸). One must then seek for some other underlying pathologic process. This is accomplished only with great difficulty, in that the reactions of the parenchyma of the brain and the perivascular connective tissue to inflammatory, toxic and traumatic irritants are similar and at times impossible to differentiate. Coupled with this handicap is the fact that there is no definite way of determining the age of a lesion in the brain.

Many authors explain the idiopathic types of encephalitis on a congenital or hereditary basis, a poor endowment resulting in a susceptibility

From the Department of Pathology, Cook County Hospital, Dr. R. H. Jaffé, Director.

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of the substance of the brain to infections and intoxications. That some children are more susceptible to cerebral involvement than others there can be no doubt. That hereditary and congenital factors play a rôle is also plausible. The susceptibility more probably results from the injuries of the brain inevitable to the vicissitudes of labor.

In the three cases to be described, which occurred in one family, the relation of injuries sustained at birth to encephalitis was demonstrated.

REPORT OF CASES

CASE 1.—A colored boy, aged 2 years, was admitted to the pediatric service because of convulsive seizures and vomiting of two days' duration. The former was manifested by spasms of the arms, culminating in attempts to tear his face or to attack any one within reach. He never lost consciousness and recovered promptly. In the last few days he had vomited, but the exact nature of the vomiting could not be ascertained.

The past history revealed that the child had been hospitalized four months before for nervousness and vomiting. At that time no definite diagnosis was made, the central nervous system not being considered.

The child was one of twins who had been delivered at home. The birth history will be considered later.

The patient was fairly well nourished; he exhibited purposeless movements and appeared listless. The temperature was 100 F.; the pulse rate, 110 per minute. The neck was rigid; there was a positive Brudzinski sign. There was impairment of resonance in the bases of both lungs; the spleen was slightly palpable, and there was a generalized lymphadenopathy.

The spinal fluid was under moderately increased pressure; it was clear, and gave a negative reaction to the Pandy test. The cell count was 40 per cubic millimeter, of which 58 per cent were lymphocytes. The Wassermann reaction of the spinal fluid was negative. The white blood count was 9,600 per cubic millimeter; the hemoglobin was 70 per cent. A differential count revealed 54 per cent polymorphonuclear leukocytes, 38 per cent lymphocytes, 5 per cent eosinophils and 3 per cent monocytes. Urinalysis gave negative results, and the Pirquet reaction was positive.

The diagnosis was not certain. Encephalitis and tuberculous meningitis were considered.

During the short stay in the hospital (seven days), the child was persistently semiconscious.

The thymus weighed 10 Gm.; it was a light purple-gray and parenchymatous. The heart weighed 50 Gm.; the chambers were dilated, and the myocardium was soft and friable. The lungs were distended, with focal areas of atelectasis in the lower lobe of the right lung. The spleen weighed 20 Gm.; the upper pole was adherent to the diaphragm. The pulp was purple-gray and friable; follicles and trabeculae were distinct. The liver weighed 370 Gm.; it was yellowish brown and had obscure markings. The peribronchial, peritracheal, mesenteric, peripancreatic and axillary lymph nodes were uniformly enlarged to 10 mm. in diameter, soft and grayish pink.

The essential changes were in the brain. The weight was 935 Gm. The leptomeninges were thin and slightly injected and were separated by an increased

amount of fluid. The consistency of the brain was firm, and the gyri, especially those of the frontal lobes, were narrower than normal. The general appearance of the brain resembled a formaldehyde-fixed organ.

Microscopic Changes in the Brain.—In the frontal lobe, the leptomeninges over the convexity were thickened by fibrous tissue and infiltrated by loosely scattered polymorphonuclear leukocytes and round cells. The subarachnoid space over the gyri was obliterated, and often the pia seemed to fuse with the subpial portions of the cerebral cortex. In the region of the sulci, the subarachnoid space was wide,

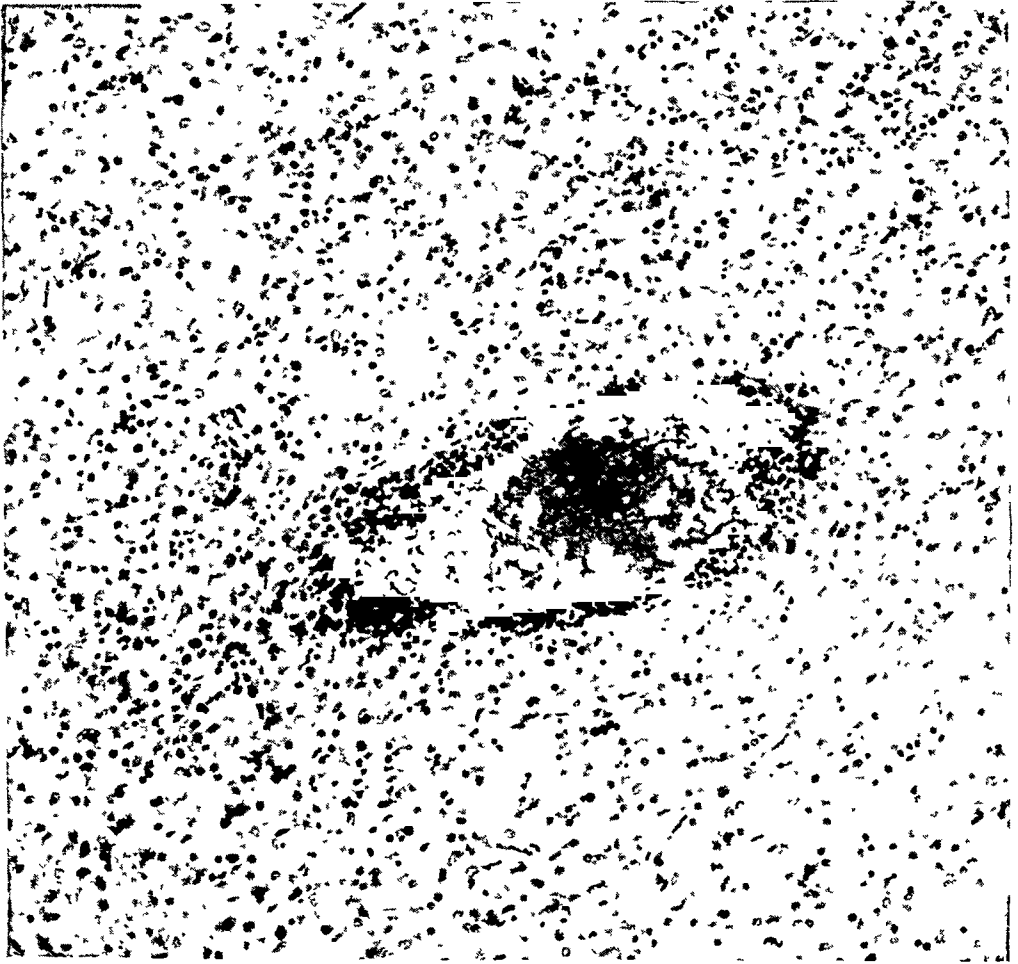


Fig. 1 (case 1).—Perivascular accumulation of round cells and polymorphonuclear leukocytes in globus pallidus; $\times 250$.

and the cellular elements were numerous. They consisted mainly of round cells, polymorphonuclear leukocytes and large mononuclear cells.

The molecular layer of the cortex was very cellular, with marked vascularity and proliferation of new capillaries. In the deeper layers, there was a marked increase in the number of oligodendroglia nuclei, which at times were so numerous as to obscure the cyto-architecture. These cells arranged themselves about or in the ganglion cells. The latter showed acute degenerative changes, with swelling, chromatolysis, vacuolation of the cytoplasm and disappearance of the nuclei. Only rarely was a calcified ganglion cell noted.

The medulla, especially in the subcortical region, showed an increase in cellularity of the protoplasmic glia and to a less extent of the microglia. There were small perivascular and interstitial glia nodules.

The changes in the parietal lobe were similar in extent and amount to those in the frontal lobe.

The histologic changes in the occipital lobe were similar to those in the frontal lobe, but were decidedly less extensive.

Beneath the ependyma of the caudate nucleus there was a marked proliferation of glia nuclei and fibers. Small hemorrhages were found in the Virchow-Robin spaces and in the spaces of His. The blood vessels in the vicinity were surrounded by oval and round cells, many of which contained iron and fat. The acute degeneration of the ganglion cells previously described was also found in this region. Many of the vessels in other localities were surrounded by thick coats of small round cells and polymorphonuclear leukocytes. Small irregular glial rosettes, as well as small calcified bodies, were found in the interstitial tissue.

In the pons, the leptomeninges were thickened and cellular, as over the frontal lobe. Along the medial longitudinal fasciculus were large nodules measuring up to 2 mm. in diameter, which were composed of small oval and round cells filled with fat. Numerous dilated capillaries were seen coursing through these nodules. The vessels in the vicinity were cuffed by numerous fat-filled cells. There were no leukocytes present.

In the cerebellum, the changes in the meninges were similar to those described. The molecular zone was markedly vascular with capillary proliferation. The substantia nigra and the cornu ammonis showed no striking changes.

CASE 2.—A colored girl, aged 3 years, the twin of the patient in case 1, entered the hospital nine months later with continuous convulsions. One year before, she had been paralyzed on the left side but had recovered in a few months. Since then she had had severe headaches on and off, but was apparently well until four hours before admission, when continuous convulsions developed.

The patient had had measles, whooping cough and chickenpox. She had been deaf and dumb since birth.

The child was well nourished and well developed. She was semicomatose, with continuous clonic convulsions involving the entire body and the face. There were râles in the bases of both lungs, posteriorly. Other physical findings were impossible to elicit because of the convulsions. The temperature was 99 F.; the pulse rate, 120 per minute, and the respiratory rate, 26 per minute.

The spinal fluid was under moderate pressure; it was clear, and gave a 4 plus reaction to the Pandy test; the cell count was 122 per cubic millimeter. A culture and the Wassermann reaction were negative.

The child died within a few hours after hospitalization.

The thymus weighed 16 Gm.; it was a light purple-gray and parenchymatous. The heart weighed 70 Gm.; the chambers were dilated, and the myocardium was pale and friable. Large patches of bronchopneumonia were found in both lower pulmonary lobes and in the upper lobe of the left lung. The spleen weighed 40 Gm.; the consistency was soft, and the pulp was purple-gray, with pinhead-sized follicles. The liver weighed 445 Gm.; it was pale and had indistinct markings.

The essential changes were in the brain. It weighed 1,115 Gm.; the leptomeninges were thin and moderately congested. The frontal lobes felt distinctly firmer than normal, as did the entire substance of the brain. The gross appearance simulated that of the brain in case 1.

Microscopic Changes in the Brain.—In the frontal lobe, the leptomeninges were thickened by large mononuclear cells and fibrocytes. The subarachnoid space was

widened and was filled with large round cells, many of which contained sudanophil substance. In the loosened subpial layer compound granular corpuscles were seen. The marginal zone of the cortex was vascular and cellular. In the deeper layers of the cortex, there was a marked increase of glia nuclei, especially oligodendroglia nuclei. Neuronophagia and satellitosis were so marked in places as to obscure the architecture. There were other areas in which the number of ganglion cells was diminished or there were none, with an increase of the glia fibrils and the formation of sclerotic plaques. In these areas, many of the ganglion cells were replaced by concrements staining deeply blue (with hematoxylin) and occasionally showing dendrite-like extensions. Many of these deposits contained perifocal accumulations of oligodendroglia nuclei. About and in the walls of the precapillaries and capillaries were small and large granular deposits of calcium. In some vessels, the

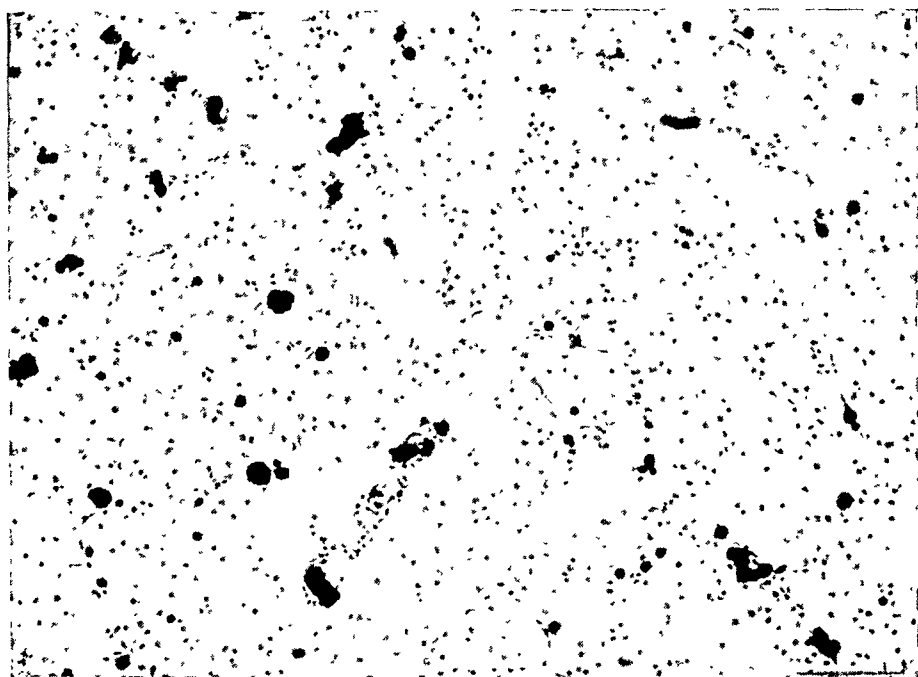


Fig. 2 (case 2).—Interstitial calcification and calcific deposits in the pericapillary spaces of the putamen; $\times 150$.

aforementioned substance was in the form of homogeneous pale blue sheets or bands. Small cavities surrounded by glia fibrils and nuclei were found especially in deeper layers.

The medulla showed less marked changes. There was a slight diffuse increase of astrocytes, glia fibrils and Hortega cells. Some of the vessels were surrounded by fat-filled cells. Here, too, small cavities were found in the subcortical areas.

In the occipital lobe, the changes were similar to those in the frontal lobe, but were less marked, especially the number of deposits of calcium.

The changes in the parietal lobe were similar to those in the frontal and occipital lobes, but were more extensive. The concrements were more numerous, and in many instances they transformed the smaller arteries and capillaries into tubes of calcium.

Throughout the entire field of the putamen and globus pallidus were scattered dark blue bodies, varying in size from that of a red blood cell to that of a large

ganglion cell. They appeared singly or in clusters. Many of the concretions had a dark blue center and were surrounded by deep blue rings of varying intensity (hematoxylin stain). The smaller arteries, precapillaries and capillaries generally were surrounded by the blue granular or homogeneous deposit or their walls contained it. The extent of involvement varied from focal accumulations in the media or the spaces of Virchow-Robin and His to complete replacement of the walls. The intima was usually spared, although rarely the entire lumen was obliterated. As a rule, there seemed to be no active cellular response to the calcium. An occasional small cavity up to 1 mm. was found which showed perifocal gliosis. The ganglion cells evidenced acute degenerative changes.

In the caudate nucleus and the internal capsule, there were deposits of calcium but they were less extensive and were concentrated about the internal capsule.

In the pons, the leptomeninges were thickened and fibrotic. Scattered about were large mononuclear cells of the histiocytic type and a few small round cells. In the parenchyma were single, perivascular nodules which were composed of cells that had elongated or indented nuclei and cytoplasm containing fine chromatin granules. At the base of the fourth ventricle were recent perivascular extravasations of blood.

Moderate cellularity and vascularity were evident in the marginal zone of the cerebellum. Some of the vessels were surrounded by fat-filled cells. The Purkinje ganglion cells were well preserved, but an occasional cell and its branches were calcified.

The cornu ammonis, substantia nigra and cervical cord showed no noteworthy changes.

CASE 3.—A colored girl, aged 6 years, was hospitalized three days following the death of her younger sister (case 2), with similar symptoms of convulsions. The mother stated that for the past year the child had shown signs of nervousness, vomiting and vague mental symptoms. The symptoms had been of sufficient intensity to warrant hospitalization one year before. The mother thought that in the past two weeks the child had had whooping cough. The cough had been continuous but nonproductive.

About one and one-half hours before admission, the child was playing, when suddenly she fell backward in an unconscious state and began having generalized convulsions. The attack lasted for twenty-five minutes, and the patient foamed at the mouth. She had been unconscious since then.

The mother was a septipara; five of the children had died as follows:

1. Died in 1925, aged 8 years; diagnosis, tuberculous pneumonia.
2. Died in 1925, aged 2 years; diagnosis, convulsive syndrome; autopsy records were not available but tuberculosis was excluded.
3. Died in 1930, aged 2 years and 9 months (case 1). }
4. Died in 1931, aged 3 years and 7 months (case 2). } twins
5. Died in 1931, aged 6 years (case 3).

The children were born at home; the births were apparently normal and at full term. The mother had had no miscarriages.

The patient sat up at 6 months, walked at 1 year and spoke words at 14 months.

The child was well nourished and semicomatose. There were continuous jerky, irregular, generalized, clonic twitchings of the entire body, but especially of the face, the neck and the upper extremities. At times the convulsions became more intense.

The temperature was 96 F.; the pulse rate was 90 per minute, and the respirations were shallow and jerky.

The eyeballs deviated from side to side in irregularly oscillating nystagmoid movements. The pupils were small, even and equal. The jaws were clenched. The reflexes were brisk, but difficult to elicit.

The spinal fluid was under increased pressure; the reaction to the Pandy test was 4 plus, and the cell count was 128 per cubic millimeter. The Wassermann reaction of the spinal fluid was negative.

The impression, in view of the previous cases in the same family, was of gliosis of the brain.

The child died within a few hours.

The thymus weighed 35 Gm., and was pale gray and parenchymatous. The heart weighed 95 Gm.; the myocardium was reddish brown and firm. The lungs were everywhere crepitant, moist and hyperemic. The spleen weighed 40 Gm.; the

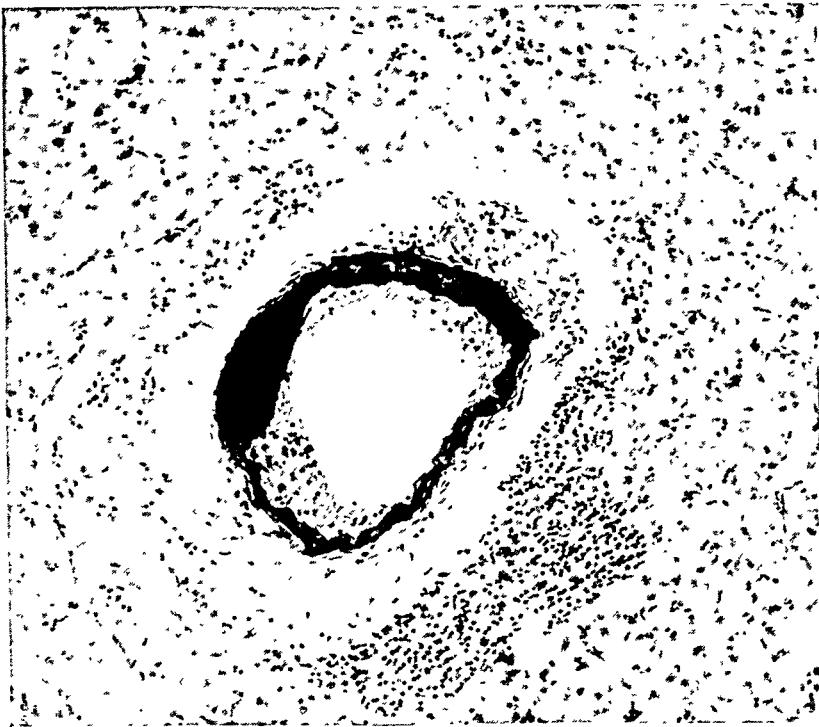


Fig. 3 (case 3).—Calcification of a small artery in the putamen. Note that the involvement is mainly of the media and adventitia, the intima being practically free; $\times 250$.

capsule was thickened, and the pulp was soft and purple-gray. The liver weighed 565 Gm.; the markings were distinct, and the parenchyma was pale.

The essential changes were in the brain. The leptomeninges over the convexity were thin, while there were slightly thickened, pale gray plaques over the base. The consistency of both cerebral hemispheres and, to a lesser extent, of the cerebellum was markedly increased. The appearance of the brain simulated that of the other two described.

The middle ears were free from abnormalities.

Microscopic Changes in the Brain.—In the frontal lobe, the leptomeninges were much thickened as a result of an increase in fibrous tissue, fibrocytes, large mononuclear cells and small round cells. In the sulci the subarachnoid spaces were

much widened and filled with similar cellular elements. Some of the histiocytic elements contained small fat droplets.

In the deeper layers of the cortex, the cyto-architecture was poorly preserved. There appeared to be focal areas of atrophy in which the number of ganglion cells was diminished or there were none, with an increase in the glia fibers. In these areas calcification of the ganglion cells was evident. (The microchemical reaction will be discussed later.) About many of these concretions were accumulations of oligodendroglia nuclei. In other places, the ganglion cells showed signs of acute degeneration. Surrounding some of the blood vessels were fat-filled cells.

The white matter showed a generalized increase of astrocytes, oligodendroglia and Hortega cells. Occasionally there were small cavities in the subcortical area.

In the occipital lobe, the leptomeninges were thickened, as over the frontal lobe. The cortical and medullary findings were also similar, but less marked.

Although the changes in the parietal lobe were similar to those in the frontal lobe, the calcification of the ganglion cells and the blood vessels was more extensive.

Deposits of calcium were found in the putamen and the globus pallidus. Scattered throughout were irregular glia nodules which were not related to vessels. In other places, small cavities were surrounded by glia fibrils. The walls of some of these cavities contained free or intracellular fat. About the vena terminalis beneath the ependyma were perivascular accumulations of glia nuclei, especially Hortega cells. Many of the latter contained a light brown pigment.

In the pons, the leptomeninges were much thickened by fibrillar connective tissue, histiocytes and large mononuclear cells. Some of the histiocytes contained small concretions of calcium. The vessels were surrounded by coats of small round cells. In the substance of the brain beneath the leptomeninges were small focal accumulations of round cells.

The marginal zone of the cerebellum was vascular with many branched capillaries.

The cornu ammonis and substantia nigra showed no noteworthy changes.

Levaditi preparations were negative for *Spirochaeta pallida*.

GENERAL REVIEW OF OBSERVATIONS

Clinical Findings.—There were many similarities in the three cases reported. The history of the child who died in 1925 at the age of 2 years resembled that of the patients in the cases reported, but the observations made at autopsy were not available except that tuberculosis was excluded. (An older child died the same year of tuberculous pneumonia.)

The cases were characterized by repeated attacks of symptoms referable to the central nervous system. The onset was insidious, with symptoms of slight headache, nervousness and vomiting, so that attention at first was not drawn to the brain. The actual attacks were more acute, with paralysis in the first case and extreme nervousness and vomiting in the first and third cases. The terminal syndrome was most severe, with semiconsciousness and convulsions.

The physical findings, when it was possible to elicit them, showed a hypertonic state with active reflexes, meningeal irritation in case 1 and nystagmus and trismus in case 3. The temperature was not characteristic, being slightly elevated in cases 1 and 2 and subnormal in case 3 (terminal state). The patient in case 2, in addition, had bronchopneumonia.

The laboratory findings were not constant. The spinal fluid was under slightly increased pressure; the cell count varied from 40 to 128 per cubic millimeter; the reaction to the Pandy test was positive in cases 2 and 3. The blood findings were not abnormal. The Wassermann reactions of the spinal fluids were negative.

Postmortem Observations on the Brain.—Macroscopically, the leptomeninges appeared only slightly congested, and at the base, as a rule, they were thickened and pale gray. The cerebral hemispheres in the three cases were distinctly smaller and firmer than normal. In case 1, the gyri of the frontal lobe were especially narrow.

In the other organs there were changes suggesting a moderately intense intoxication or infection. In case 2 there was frank bronchopneumonia of long duration.

Microscopically, case 1 presented changes somewhat different from those in cases 2 and 3, although both groups were characterized by older and more recent lesions.

In case 1, the intensity of the pathologic changes varied in the different regions of the brain in the following order: pons, central ganglion (caudate nucleus, globus pallidus and putamen), cortexes of the frontal, parietal and occipital lobes and medullary portions of these lobes. The recent changes were characterized by acute degeneration of the ganglion cells, rarefaction and hemorrhages; proliferation of the capillaries and of the cellular glia, both perivascular and in rosettes, and perivascular accumulations of lymphocytes and polymorphonuclear leukocytes. The more chronic alterations were the proliferation of the glial fibrils, the fibrous tissue proliferation of the leptomeninges and finally the nodules composed of fat-filled cells, proliferated glia and capillaries.

The changes in cases 2 and 3 were somewhat similar. The most intense involvement was in the putamen and globus pallidus, and then in the cortexes of the parietal lobe, frontal lobe and occipital lobe, the medullary portions of these lobes, the pons, the caudate nucleus and the internal capsule. The acute degeneration of the ganglion cells and the rarefaction were decidedly less marked than in case 1, and hemorrhages were found only in case 2. Proliferation of the cellular glia was extensive, but lymphocytes were rare and granulocytes absent.

Irregular glia nodules¹³ were found in the putamen and globus pallidus in case 3. These advanced changes superseded the acute ones. Decrease to absence of ganglion cells in the focal areas, with scar formation, in the cortex and calcification of ganglion cells, as well as small arteries, precapillaries and capillaries, predominated. Small cavities were found in the globus pallidus, putamen, cortex and subcortical zone of the medulla. Many of the cavities showed a perifocal increase of glia fibrils, and their peripheries contained free or fat-filled cells. The meninges, especially in case 3, presented fibrosis, which was most marked at the base.



Fig. 4 (case 3).—A sclerotic plaque in the cortex of the parietal lobe. Note the calcified ganglion cells about the sclerotic area. Toluidine blue stain; $\times 50$.

MICROCHEMICAL REACTIONS OF CONCRETIONS IN THE BRAIN

The concretions free in the parenchyma and in the ganglion cells stained deeply with hematoxylin or hemalum. In some instances concentric rings were noted about a dark blue center. In the vessels the staining reactions varied from a diffuse, homogeneous, pale blue to a coarsely to finely granular dark blue. With toluidine blue, the concretions usually stained deep blue, but at times were not stained by this method. With sudan III, the reaction was negative.

13. The glia nodules were distinctly different from the focal germinal areas commonly found in the brains of small children.

Calcium Reactions.—With the addition of acid, small gas bubbles formed underneath the cover glass.

With the method of Roehl, the concretions stained intense violet.

An interesting observation was that in the stained preparations (with hematoxylin and eosin), the application of a 5 per cent solution of nitric acid resulted in a dissolution and decolorization of the majority of the concretions, with the formation of small gas bubbles, but here and there some of the concretions did not become decalcified or decolorized. Furthermore, after being washed thoroughly with water and stained with Ehrlich's or Böhmer's hematoxylin, most of the decalcified deposits stained blue. This was also the case with the vessels.

Iron Reactions.—Perl's reaction was positive in the walls of the calcified vessels and with the concretions in the region of the central ganglion, but only occasionally positive in the calcified ganglion cells of the cortex.

Optic Reactions of the Concretions of Calcium.—Dark-field and polariscopic methods showed no refraction.

After decalcification the bodies were refractile and glistening.

INTERPRETATION OF THE PATHOLOGIC CHANGES

From a microscopic standpoint, the determination of the age of a lesion in the brain is extremely difficult. The inflammatory changes in this organ, for instance; are in no way parallel to the duration of the disease (Spatz,¹⁴ Jacob,¹⁵ Spielmeyer¹² and others). Disease processes may disappear quickly or may remain for years. Thus, relatively acute changes were found in the brain by Jacob after four years, by von Economo¹⁶ and Goldstein¹⁷ after two years, by Spielmeyer after one year and by Spatz after four months. In many instances, one must resort to the history for an accurate determination of the age of a lesion (Wohlwill¹⁸). There are, however, some gross and microscopic features which suggest chronicity.

In all three cases cited, the gross appearance of the brain spoke in favor of a long-standing process, i. e., the firmness of the cerebral hemispheres, the atrophy of the convolutions and the absence of marked hyperemia.

14. Spatz, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **77**:261, 1922; Encephalitis, in Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7.

15. Jacob, Alfons: Normale und pathologische Anatomie und Histologie des Grosshirns, Vienna, Franz Deuticke, 1927.

16. von Economo, Constantin: Die Encephalitis lethargica, ihre Nachkrankheiten und ihre Behandlung, Berlin, Urban & Schwarzenberg, 1929.

17. Goldstein, K.: Ztschr. f. d. ges. Neurol. u. Psychiat. **76**:627, 1922.

18. Wohlwill, F.: Klin. Wchnschr. **5**:805, 1926.

Microscopically, in the first case some lesions were much older than others. Thus, the fibrous thickening of the meninges and the nodules of fat-filled cells in the pons were older than the perivascular accumulations of lymphocytes and polymorphonuclear leukocytes in the globus pallidus and the putamen. The granulocytic and round cell infiltrations of the fibrous meninges suggested that an acute process had been superimposed on a chronic healed one, for there was no intermediary stage of proliferation and plasma cells, histiocytes and fibrocytes. Many of the chronic changes in the brain proper were undoubtedly obscured by the acute process.

The changes in cases 2 and 3 similarly suggested the superimposition of an acute process on a chronic one. The small cavity formation and the atrophic, sclerotic plaques in the cortex were compatible with a long-standing process, in many instances arrested. The calcification also substantiated chronicity, although Jacob believes that it may occur in acute lesions. On the other hand, the acute degeneration of the ganglion cells, the perivascular accumulation of glia nuclei and the interstitial nodules resembled an acute process, as was indeed brought out by the history.

It appears, then, that in the three brains there was an underlying chronic process on which was superimposed an exudative lesion in the first case and a degenerative lesion in the second and third cases.

What is the pathogenesis of the primary chronic process, and what is the nature of the complications?

PATHOGENESIS OF THE PRIMARY PROCESS

In 1867, Virchow¹⁹ described small yellow nodules in the medulla of the cerebral hemispheres of new-born infants which microscopically were composed of groups of fat-laden cells. Because some of the cells were swollen and others proliferated, simulating the cellular reaction in inflammation, Virchow believed that the condition was infectious, designating it as "interstitial encephalitis of the newborn." Etiologically, he considered syphilis and the acute exanthems, especially small-pox. In 1871, Jastrowitz²⁰ reported that the appearance of fat-laden cells in the medullary portion of the cerebrum was a normal physiologic process up to the eighth month and was related to the formation of the myelin sheath. On the strength of this work, Virchow published a second paper in 1883 in which he conceded that the condition which he had described might not be infectious, but at any rate was of a progressive character. The matter lay dormant until recently (1920),

19. Virchow, R.: *Virchows Arch. f. path. Anat.* **38**:129, 1867; *Berl. klin. Wchnschr.* **19**:706, 1883.

20. Jastrowitz, M.: *Arch. f. Psychiat.* **3**:162, 1871.

when the entire subject was again opened, and a middle stand was taken by Ceelen,²¹ Wohlwill¹⁸ and others, in that they believed that the fat in question was either anabolic or catabolic, the latter usually resulting from infection (von Limbeck,²² Ceelen,²¹ Schmincke²³). Shortly afterward, Schwartz,²⁴ Siegmund²⁵ and Gross²⁶ (1922) took the stand that the presence of fat in the brain was always pathologic, and they agreed with Parrot²⁷ (1868) that it was the result of trauma sustained at birth.

Schwartz²⁴ stated in his excellent paper that even in so-called normal deliveries, the difference between the intra-uterine pressure (after rupture of the bag of waters) and the atmospheric pressure is so great that destructive changes affecting the head (especially if lowest in the pelvis) are inevitable. The decreased pressure in the region of the brain at times causes the blood to rush there with sufficient force to rupture blood vessels. Of equal importance is the pressure exerted on the substance of the brain, which almost always shows the effects of such insults.

The same author, in studying the brains of animals (calves, rabbits, dogs, cats, hogs and chickens), found that without the stresses and strains of labor the brains of the new-born do not show fat in the nerve substance, the interstitial tissue and the ganglion cells. One may find a few fat-laden cells along the blood vessels in such cases. After a so-called normal delivery, only a small percentage of animals and human beings have normal brains, as described.

In the majority of the new-born there are some changes in the brain following labor, a fact not difficult to conceive considering the soft skull and watery brain. According to Schwartz,²⁴ the milder types of lesions consist in (excluding hemorrhages) a loosening of the substance of the brain, and, if more extensive, a vacuolation of this substance. When loosening occurs, the lesion remains stationary for from three to four days. About the fifth or sixth day, necrosis sets in, with destruction of the ganglion cells, axis cylinders, glia and other elements. By the sixth or eighth day, fat-laden cells appear, and organization begins. This organization may take from months to years; the fat is removed, the glia proliferates, and a small scar results which may be difficult to find. A similar process takes place in the reparation of vacuolation

21. Ceelen, W.: *Virchows Arch. f. path. Anat.* **227**:152, 1920.

22. von Limbeck, R.: *Ztschr. f. Heilk.* **7**:87, 1886.

23. Schmincke, A.: *Ztschr. f. d. ges. Neurol. u. Psychiat.* **60**:290, 1920.

24. Schwartz, P.: *Ergebn. d. inn. Med. u. Kinderh.* **31**:165, 1927.

25. Siegmund, H.: *Klin. Wchnschr.* **1**:2274, 1922; *München. med. Wchnschr.* **70**:137, 1923.

26. Gross, W.: *Centralbl. f. allg. Path. u. path. Anat.* **33**:225, 1922.

27. Parrot, J.: *Arch. de physiol. norm. et path.* **1**:622, 1868.

of the substance of the brain. Small vacuoles may be replaced by scar formation, but larger ones remain as cavities surrounded by glia fibrils. In the latter, deposits of calcium and of iron may be found. Schwartz designates the stage in which accumulations of fat are seen as "presclerotic," and the stage of gliosis and scar formation as "sclerotic."

These lesions may occur in any portion of the brain. Most commonly, however, they are found in the frontal and occipital medullary portions, in the part drained by the vena terminalis and vena lateralis and in the basal ganglions, cortex and medulla oblongata.

The late stages may be summarized as follows: (1) decrease of cell masses in the areas of scarring; (2) hardening of the brain substance as a result of the production of glia fibrils; (3) disturbance of the architecture of the cells through degeneration, with disappearance and calcification of the ganglion cells and accumulations of granulations between organizing glia cells; (4) disturbance of the architecture of the medulla as a result of degeneration of nerve fibers and replacement by scar tissue; (5) resulting small cavities consequent to vacuolation of nerve substance, and (6) small, especially firm scars resulting from small loosened areas.

Although, in the main, the work of Schwartz has been accepted (Ylppö,²⁸ Wohlwill,¹⁸ Seitz,²⁹ Mayer,³⁰ Siegmund,²⁵ von Kruska³¹), there are important features which are held open to question. Wohlwill, for instance, accepts the more extensive lesions following trauma sustained at birth, which are manifested clinically by paralysis, nystagmus, idiocy and epilepsy, but takes a neutral to negative stand concerning the milder types of lesions, with few or no clinical symptoms, and the microscopic appearance of "presclerosis" or "sclerosis." This author believes that clinical manifestations offer the better basis for judgment, a point which must be conceded. But what is difficult to understand is why the milder involvements are so strenuously attacked, if such extensive lesions as microgyria, porencephaly, lobar atrophy and sclerosis are accepted as traumatic complications sustained at birth and are compatible with adult life. It appears more logical to assume that the milder lesions should be more common than the severe ones, and it is perhaps because of difficulty in recognition or because of overshadowing by some complication that they are not found.

In the three cases described, the underlying chronic lesions presumably had their origin in trauma at birth. In the first case, the

28. Ylppö, A.: *Ztschr. f. Kinderh.* **20**:212, 1919.

29. Seitz, L.: *Arch. f. Gynäk.* **82**:528, 1907.

30. Mayer, A.: *Zentralbl. f. Gynäk.* **39**:795, 1915.

31. von Kruska, B. G. T.: *Ueber Geburtsläsionen der Gehirnssubstanz, speziell die ischämischen Nekrosen und ihre Folgezustände*, Inaug. Dissert., Halle, 1915.

presclerotic stage was seen, but sclerotic manifestations were probably obscured by the more acute process. In the second and third cases, the presclerotic, but more markedly the sclerotic, stages were evident. That these children were especially exposed to injuries at birth can be judged by the following facts: The children were colored and it is a long-established fact that colored women most frequently have contracted rachitic pelves. The patients in cases 2 and 3 were twins, which speaks for increased insults at birth (Wohllwill¹⁸). Three of seven children (and probably a fourth) presented rather similar clinical and pathologic changes, with nervous symptoms dating back from four months to one year. (As will be discussed later, the symptoms were probably of longer duration.)

PATHOGENESIS OF SUPERIMPOSED EXUDATIVE LESION IN CASE 1

One of the most difficult problems in neuropathology is the microscopic differentiation of inflammatory from noninflammatory conditions. Indeed, the reactions at times are so similar that the distinction from a microscopic standpoint is only nominal, being dependent on bacterioscopic and cultural findings and animal inoculations. Thus one distinguishes an "inflammatory reaction" (Spatz¹⁴), an "encephalitic symptom complex" (Spielmeyer¹²) or "encephalopathy" (Aschoff³²) from an inflammatory disease" (Spatz¹⁴) or "true encephalitis" (Spielmeyer,¹² Aschoff³²) more by the bacterioscopic studies than by histologic characteristics. Unfortunately, even the bacterioscopic findings and the animal inoculations may be negative in obvious inflammatory diseases.

In the first group of cases, the pathologic changes underlying the "inflammatory reaction" may be found, such as hemorrhages and areas of softening. In the second group of cases, the predominance of cellular infiltration, especially granulocytes, and the relatively small number of granule cells may aid in the diagnosis. In both groups, however, the basic reactions are similar, i. e., a cellular infiltration (leukocytes, lymphocytes, mast cells, plasma cells and macrophages), in addition to a reaction of the glia.

The difficulty in deciding the etiology of the infiltrating reaction in case 1 is at once apparent, especially since no animal inoculations were carried out (cultures of the spinal fluid were negative). Yet there were certain paramount features which spoke in favor of an "inflammatory disease." In the regions in which the reparative lesions were found (pons), the granule cells were numerous both in the direct vicinity and about the more remote vessels. Granulocytes were not found in this region, and lymphocytes were rare. In distant parts (putamen, globus pallidus) devoid of presclerotic areas, the perivascular infiltra-

32. Aschoff, L.: Beitr. z. path. Anat. u. z. allg. Path. **71:19**, 1922.

tions consisted of many lymphocytes and polymorphonuclear leukocytes, but few granule cells. The leukocytic infiltration of the meninges was also suggestive of an inflammation.

In many respects, the foregoing histologic picture simulates epidemic encephalitis. Early in this condition (from the second to the third day) perivascular and meningeal leukocytes appear (von Economo,¹⁶ Spatz,¹⁴ Bassoe and Hassin³³) among the other infiltrative elements. The irregular glia nodules ("fleckförmig") not associated with vessels were found in case 1. The location of the process, however, was dissimilar. Whereas in epidemic encephalitis the nucleus caudatus and putamen are usually spared (von Economo,¹⁶ Spatz,¹⁴ Ernst), in the case described, the putamen and globus pallidus were the sites of predilection.

The other types of true encephalitis listed by Wohlwill¹⁸ as occurring in children may be excluded as follows: encephalitis in association with meningitis, because the changes in the brain were older and more severe than the changes in the meninges, although clinically meningeal irritation was evident; encephalitis associated with acute infectious diseases, because of the negative history and postmortem observations; purulent encephalitis, because of the absence of suppuration; polioencephalitis haemorrhagica superior of Wernicke and purpura of the brain of other etiology, because of the absence of extensive ring hemorrhages and vascular proliferation in the midbrain; encephalitis degenerativa or encephalitis congenita, already discussed. The latter three types of encephalitis should be considered as pseudo-encephalitis ("inflammatory reaction," Spatz¹⁴).

There remains to be explained, then, the acute manifestations in case 1, a superimposed inflammatory disease secondary to a cryptogenic focus not disclosed by the history or by the postmortem observations or an atypical form of epidemic encephalitis. That the entire process is one of epidemic encephalitis is unlikely, because of the clinical history and the absence of scarring and a decrease in the size of the black zone, the substantia nigra (Goldstein,¹⁷ Jacob,¹⁵ Spatz,¹⁴ Wilckens⁷).

PATHOGENESIS OF THE DEGENERATIVE PROCESS OR INFLAMMATORY REACTION IN CASES 2 AND 3

The absence of granulocytes does not necessarily exclude true encephalitis, but the large degenerative zones and the presence of many granule cells laden with fat and pigment suggest an inflammatory reaction rather than disease. This process, although still active, suggested chronicity, because of the cavity formation, the atrophic areas in the cortex and the calcification. In many places arrested lesions

33. Bassoe, P., and Hassin, G. B.: Arch. Neurol. & Psychiat. 2:24, 1919.

were evident, as cortical scars or deposits of calcium without an active glial response. Yet the presence in other localities of marked acute degeneration of the ganglion cells with glial proliferation, perivascular and in nodules, suggested a more recent toxic agent. This was borne out by the clinical history, in that the children, although having clinical manifestations related to the central nervous system for one year, appeared much improved, and then were suddenly taken ill and shortly afterward died with symptoms of acute cerebral disturbance.

The cause of the exacerbation in the second case may be related to the extensive bronchopneumonia, while that in the patient in the third case, who lived in the same house, might be explained similarly, except that in the latter only an infection of the upper respiratory tract developed, as was manifested clinically by cough. The mother interpreted the cough as of the whooping character, but this could not be substantiated in the hospital or anatomically. This possibility was not entirely ruled out, as the acute degeneration of the ganglion cells in the cortex, especially in the parietal lobe, might well be explained by a whooping cough encephalitis (Spielmeyer¹²), but the absence of the linear arrangement of the cells in the cornu ammonis as well as ring hemorrhages (in the eclamptic form) suggested another etiology.

It is more likely that the bronchopneumonia on the one hand and the infection of the upper respiratory tract on the other were responsible for the inflammatory reactions being superimposed on an already damaged brain.

RELATIONSHIP OF TRAUMA SUSTAINED AT BIRTH TO ENCEPHALITIS

Experimentally, the injection of bacteria into the carotid artery or the aorta rarely produces encephalitis, and then only in brains that have been injured in one way or another (Lamy⁸). The injection of small emboli with the bacteria produces lesions in the brain with greater frequency (Lhermitte and Schaeffer³⁴). The latter phenomenon is explained by the fact that the embolus injures the substance of the brain so that the organisms come in direct contact with the parenchyma. Thus, the injection of bacteria directly into the substance of the brain invariably leads to encephalitis (Homén³⁵).

Applied to man, isolation of bacteria from cerebral vessels in cases of streptococcic, staphylococcic and pneumococcic septicemia is accomplished in 75 per cent of cases (E. Frankel⁸); yet encephalitis in these instances is rare. In vegetative or verrucous endocarditis, the incidence of encephalitis is much higher (Spatz,¹⁴ Diamond³⁶), partly because

34. Lhermitte, J., and Schaeffer, H.: *Semaine méd.* **30**:25, 1910.

35. Homén, E. A.: *Arb. a. d. path. Inst. zu Helsingfors* **2**:1, 1919.

36. Diamond, I. B.: *Arch. Neurol. & Psychiat.* **27**:1175, 1932.

of the associated emboli. Also, it is common knowledge that encephalitis may follow injuries to the head, in which a mild infection of the upper respiratory tract may initiate the disease. Indeed Aschoff has repeatedly demonstrated such cases at his pathologic conferences.

In other parts of the body, the relationship between injury and inflammation is a long-established fact (osteomyelitis, tuberculosis of the bone and the lungs). Yet little stress is placed on the association of such widely prevalent and at times extensive lesions as traumatic injuries sustained at birth with inflammatory or toxic conditions of the brain and spinal cord. There can be no doubt that the brain, thus injured, is a focus of lowered resistance and a prey for bacteria and toxins.

The first case reported demonstrated an inflammatory process, while the second and third cases showed toxic ones, superimposed on traumatic lesions sustained at birth. The attacks, as described clinically (transient paralysis, vomiting, mental disturbances), demonstrate the susceptibility of the brains of such persons to infections and toxic irritants.

One should inquire more thoroughly into the encephalitis of unknown origin, the atypical and sporadic types of epidemic encephalitis with clinical signs of hemiplegia or diplegia and, finally, the toxic forms of encephalitis in which the etiology is obscure or follows a pyogenic focus. It is likely that in many of the foregoing instances the underlying pathogenesis has its origin in a trauma sustained at birth, and that the toxic or inflammatory irritants, obvious or obscure, virulent or avirulent, find a devitalized, susceptible ground for their activities. It must be borne in mind that the more acute process may easily overshadow the chronic one.

PATHOGENESIS OF CALCIFICATION IN THE BRAIN IN RELATION TO TRAUMA SUSTAINED AT BIRTH

Calcific changes in the brains of children are rare (Jores, Jacob¹⁵). They have been described as associated with traumatic lesions sustained at birth, including so-called Virchow's interstitial encephalitis (Parrot,²⁷ Schmincke,²⁸ Schwartz²⁴); with carbon monoxide poisoning (Herzog,³⁷ Wohlwill¹⁸); with epidemic encephalitis (Dürck,³⁸ Siegmund²⁵); with tetany (Schnabel,³⁹ Ostertag⁴⁰); with mongolian idiocy (Jacob,¹⁵ Ostertag⁴⁰), and with conditions of unknown etiology

37. Herzog, G.: München. med. Wchnschr. **22**:558, 1920.

38. Dürck, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **72**:175, 1921; Verhandl. d. deutsch. path. Gesellsch. **18**:88, 1921.

39. Schnabel, H.: Centralbl. f. allg. Path. u. path. Anat. **33**:226, 1922.

40. Ostertag, B.: Virchows Arch. f. path. Anat. **275**:828, 1930.

(Sauer ⁴¹). Many of the cases in which calcification is reported, however, must be considered with skepticism, because there appears in brains at all ages as a supposed incidental finding a noncalcium-containing substance which simulates calcium in morphology and in location.

In the older literature, these deposits were considered as pathognomonic of chorea (Elischer,⁴² Flechsig⁴³), and from time to time they are rediscovered in other diseases. More recently these bodies have been found in 72 per cent of the brains of patients dying of various diseases and at all ages (Kodama,⁴⁴ Ostertag⁴⁰).

Similar to the concretions of calcium, this pseudocalcium (Spatz,¹⁴ Ostertag⁴⁰) appears in the brain in three forms: (a) free in the tissue, as small granules which may become confluent, assuming the shape of a mulberry; (b) in the same form, but about the walls of the capillaries, sometimes replacing the capillary wall and obliterating the lumen; (c) in the walls of arteries, appearing as homogeneous or granular masses.

In regard to location, calcium and pseudocalcium are found most frequently in the globus pallidus and the putamen. In the cases reported, deposits of calcium were frequently seen replacing ganglion cells and in the walls of the vessels of the cortex, a property not described as common to pseudocalcium.

Calcium and pseudocalcium both have an affinity for basic dyes. It is the deep blue staining with hematoxylin that confuses the two. Calcium gives positive reactions with the Roehl and Kossa methods for calcium, whereas pseudocalcium does not. The application of dilute nitric acid yields gas bubbles with the concrements of calcium only. Another point of differentiation, as I have shown, is the application of dilute acid to sections stained with hematoxylin. The calcium becomes decolorized and gas bubbles form, whereas the pseudocalcium is not decolorized and no gas is produced.

Mallory⁴⁵ and, independently, Hansemann⁴⁶ were the first to show that there was a close relationship between pseudocalcium and calcium. By decalcifying the vessels of the brain, they found that there remained a refractile substance which had a marked affinity for hematoxylin. This fact was also noted in the cases reported, but included interstitial deposits of calcium and calcified ganglion cells. Mallory concluded that the ground substance was a colloid material and the basis for all calcification of the vessels of the brain.

41. Sauer, W.: *Ztschr. f. Kinderh.* **46**:457, 1928.

42. Elischer, J.: *Virchows Arch. f. path. Anat.* **63**:104, 1875.

43. Flechsig, P.: *Verhandl. d. Cong. f. inn. Med.* **7**:452, 1888.

44. Kodama, F., quoted by Ostertag.⁴⁰

45. Mallory, F. B.: *J. Path. & Bact.* **3**:110, 1894-1896.

46. Hansemann, H.: *Verhandl. d. deutsch. path. Gesellsch.* **2**:399, 1898-1899.

The true nature of this colloid, as of colloids in general, is not known. It is insoluble in alcohol, ether and chloroform, and reactions for glycogen and amyloid are negative (Ostertag⁴⁰). The addition of water or a weak alkaline solution causes this substance to swell and lose its glistening and refractile properties. Perl's reaction for iron is rather constant (Perusini⁴⁷), especially if concentric rings are present (Ostertag⁴⁰). However, this property is dependent on the presence of iron in the vicinity (Spatz¹⁴). In children, the colloid gives a positive reaction only if iron has appeared in the brain (Spatz¹⁴). Thus the colloid in the region of the central ganglions in cases 2 and 3 gave a positive reaction for iron (Perl's) because of the abundance of iron there, but that in the region of the cortex gave such a reaction only rarely, because of the paucity of iron there. The vessels, wherever calcified, gave this reaction.

That the blue staining of the colloid with hematoxylin might be explained as a result of the iron content (Wells⁴⁸) must be borne in mind. In such instances, however, the hematoxylin stains lightly. As reported, the colloid stained deeply with hematoxylin, and iron was rarely demonstrated in the deposits in the cortical ganglion cells, although the strong affinity for the basic dyes remained.

The pathogenesis of this colloid substance is even less clearly understood. It is believed to occur when there is an alteration of the tissue metabolism and when the tissue fluids become stagnant and are precipitated. Thus it is seen at the junction of healthy and diseased tissues, as in cases of tumors, dementia paralytica, amaurotic family idiocy and other conditions. Similarly, Ostertag⁴⁰ explains the occurrence of the colloid bodies at the junction of the globus pallidus with the internal capsule and putamen as the result of a change in the type of metabolism. Why there should be such a change at this point only has not been clearly ascertained.

When one considers the positive factors concerning the deposit of calcium and compares them with the salient features of traumatic lesions sustained at birth, a more likely explanation is evident. First, the occurrence of the deposit at the junction of diseased or degenerated and healthy tissue corresponds closely to the site most commonly affected in injuries sustained at birth, namely, the region of the internal capsule. Second, the high incidence of colloid bodies reported by Kodama⁴⁴ and Ostertag⁴⁰ (72 per cent) corresponds to the high incidence of traumatic lesions sustained at birth.

What possibly takes place is that with the destruction of the tissue of the brain following insults at birth, much colloid substance is liberated. The latter remains locally or is transported by the tissue fluids

47. Perusini, G.: *Folia neuro-biol.* 6:465, 1912.

48. Wells, H. G.: *Arteriosclerosis*, to be published.

or cellular elements to the perivascular spaces (the spaces of Virchow-Robin and of His). Because of the great affinity of elastic fibers for colloids (also mucin and calcium, Wells⁴⁸), much of the colloid substance becomes deposited between the elastic fibers of the arteries. The veins having less elastic tissue are less frequently affected. In the perivascular spaces about the capillaries a stagnation occurs. The fate of the stagnant colloid is similar to the aging of colloid in general. This is characterized by a tendency to dehydration, a decrease in the degree of dispersion of the particles and the formation of larger particles which are less stable (Wells⁴⁸). The homogeneous and granular deposits, as described in the text, may be explained by the latter mechanism. That such aging may come about in a relatively short time is readily seen by the changes occurring in the placenta, which becomes typically senile in nine months (Warthin,⁴⁹ Wells⁴⁸).

It is with this stagnant, degenerating colloid as a basis that calcification sets in. According to the available evidence, calcium salts exist in the body fluids in three forms: in combination with proteins, in an ill-defined form which depends on parathormone (Greenwald⁵⁰) and as simple inorganic ions in solution (Barr⁵¹). It is generally agreed that the amount of calcium dissolved in the serum is greater than can be held in solution by similar concentrations of phosphorus and carbonate (Hastings, Murray and Sendroy,⁵² Holt, LaMer and Chown⁵³). Whether or not a supersaturation of calcium takes place in the serum is not definitely proved, but that the equilibrium of the solution can easily be disturbed and calcium thrown out of solution is widely accepted (Kleinmann,⁵⁴ Barr⁵¹). Such a disturbance may be local, where it depends on a chemical alteration in the tissue. The nature of this disturbance has been best described by Kleinmann,⁵⁴ who demonstrated an alkalinity in devitalized tissue. In the presence of alkalinity, the tertiary calcium phosphate is precipitated in crystalline form. The latter in turn draws the calcium and carbonate from solution in the form of a mixed precipitate of calcium phosphate and calcium carbonate. Although this theory is the most plausible, it is still open to question, as it is based on supersaturation (Barr⁵¹). That alkalinity plays a determining rôle is evident in the fact that calcium metastases are found

49. Warthin, A. S.: *Old Age: The Major Involution*, New York, Paul B. Hoeber, Inc., 1929.

50. Greenwald, I.: *J. Biol. Chem.* **117**:1, 1926.

51. Barr, D. P.: *Physiol. Rev.* **12**:593, 1932.

52. Hastings, A. B.; Murray, C. D., and Sendroy, J., Jr.: *J. Biol. Chem.* **71**:723, 1927.

53. Holt, L. E.; LaMer, V. K., and Chown, H. B.: *J. Biol. Chem.* **64**:509, 1925.

54. Kleinmann, H.: *Biochem. Ztschr.* **196**:98, 1928.

only where acid is secreted or excreted in the tissues, signifying an alkalinity in that place (Askanazy,⁵⁵ Hofmeister⁵⁶).

In summary, the pathogenesis of the calcification as seen in the cases reported was presumably dependent on the destruction of tissue resulting from injuries sustained at birth. There followed a liberation of colloid materials, which either remained locally or were carried to the perivascular spaces. Of the latter, part was carried away by the blood stream, part was attracted by elastic fibers of the arteries, and part remained stagnant in the pericapillary spaces. Owing to the stagnation, this colloid aged rapidly. Some of the colloid fell out of solution and became granular. As a result of the alkalinity of this devitalized substance, the tertiary calcium phosphate was precipitated. The latter caused the calcium and carbonate to be thrown out of solution in the form of calcium phosphate and calcium carbonate.

COMMENT

The microscopic diagnosis of injuries of mild character sustained at birth is subject to much error, especially if these injuries are observed late in childhood. One of Wohlwill's¹⁸ chief criticisms of Schwartz'²⁴ work was that he found accumulations of fat-filled cells ("presclerotic stage" of Schwartz) in infants dying of grip. It is true that the early and late stages of inflammatory lesions of the brain may simulate foci due to trauma at birth. Also, sclerotic plaques and the formation of small cavities are common to both (Schwartz²⁴). One may then reason that the chronic lesion described was the result of old encephalitis. Referring, then, to the history as suggested by Wohlwill,¹⁸ it will be noted that the onset of the cerebral manifestations was insidious, with nervousness, vomiting and headaches which were so slight at first that pathologic changes in the brain were not considered. Such an onset in children would speak against encephalitis, whereas the acute attacks were typical of it. True, the time element of the symptoms does not go back to early infancy, but experience with histories from the class of colored patients coming to the Cook County Hospital has taught that such histories, at best, are inaccurate. In the first case, for instance, the child had been in the hospital four months before the second admission, and unquestionably had been ailing for some time to warrant the first hospitalization. Furthermore, many injuries sustained at birth present no clinical manifestations until late in life.

The macroscopic appearances of the brains described were singular and yet similar, suggesting a long-standing common process. Schmincke²³ described firm, grayish-white brains in a 9 month old

55. Askanazy, M.: Beiträge zur Knochenpathologie, Festschrift für Jaffé. Braunschweig, 1901.

56. Hofmeister, F.: *Ergebn. d. Physiol.* **10**:429, 1910.

infant and in a 1½ year old child. This author diagnosed the cases as Virchow's interstitial encephalitis, but, as has already been stated, they belong to the group of traumatic lesions sustained at birth. The time required for a brain to become firm, with shrinking of the gyri, is therefore not definite.

Another point difficult to explain is the assertion that in all cases both an older lesion and a recent one existed. As a rule, this assertion is not possible, and in cases 2 and 3, it might be doubted. But here again the history is suggestive of an acute attack initiated by bronchopneumonia, which was older than the duration of the encephalitic symptoms. In case 1, the leukocytic infiltration, especially of the meninges, where granulocytes and lymphocytes were present among fibrous connective tissues without the intermediary stage of plasma cells, histiocytes and fibrocytes, is a reliable indication of a superimposed acute infectious process.

SUMMARY

It has been suggested that in many cases of so-called idiopathic and atypical types of encephalitis in children the underlying cause may be the injuries sustained at birth. With the brain in a state of lowered resistance, cryptogenic or obvious infections may initiate encephalitis.

The clinical history in such cases may indicate a difficult or prolonged labor, although the morbidity in so-called normal labors is sufficient. The children may have signs referable to the central nervous system from birth, or these signs may be absent or so slight as to be overlooked. Repeated attacks of encephalitis should probably be considered pathognomonic, more especially if associated with paralysis. The temperature, spinal fluid findings and number of leukocytes in the blood depend on the severity of the superimposed infection.

The prognosis is not necessarily fatal and is dependent on the severity of the underlying injury and the virulence of the invading organism or toxin. Some of the cases in which the patient recovered described by Brain, Hunter and Turnbull,¹ Stooss² and Grinker and Stone¹¹ might fall in this group.

The macroscopic appearance of the brain may be normal if the injuries were slight, or may be altered by recent infection. In the more pronounced cases, small yellow nodules, grayish-white plaques or the formation of minute cysts may be seen. In severe injuries, the brain may be focally or diffusely firm, with shrunken gyri, most commonly of the frontal and occipital lobes. The most extensive lesions are hemorrhages, porencephaly, atrophy of the entire hemispheres or sclerosis of the hemispheres. The meninges may or may not be thickened; the falx cerebri and the tentorium cerebelli may show evidences of old rents or hemorrhages.

Microscopically, the presclerotic or the sclerotic foci, with colloid deposits or deposits of calcium and the formation of cysts, are suggestive of trauma sustained at birth. These lesions may be found in any portion of the brain, but characteristically in the frontal and occipital lobes, in the portions drained by the vena terminalis and the vena lateralis ventriculi and in the basal ganglions. The secondary process may be true encephalitis or pseudo-encephalitis.

CONCLUSIONS

A clinical pathologic syndrome of encephalitis is described in three children of one family in whom the primary condition was apparently of traumatic origin at birth, while the superimposed changes were of infectious or toxic origin.

It is suggested that many of the idiopathic and atypical forms of encephalitis in children are due to the superimposition of a mild infection or intoxication on foci of lowered resistance in the brain, secondary to insults sustained at birth.

Colloid deposits and deposits of calcium in the brains of children are explained as sequelae to injuries sustained at birth.

CONGENITAL VALVES OF THE POSTERIOR URETHRA IN TWINS

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AND

CHARLES NEWBERGER, M.D.

CHICAGO

While the number of reports of congenital valves in the posterior urethra is close to one hundred, we present, for the first time, a description of identical congenital valves in twins.

REPORT OF CASE

An octipara, aged 38, was admitted to the obstetric service of Dr. Charles Newberger on Nov. 9, 1932. All previous deliveries were normal; there had been no twins. At the time of admission the patient was in active labor; the membranes had ruptured about fifteen minutes previously. After the delivery of the first child, it was found necessary to rupture the membranes of the second child. Delivery was uncomplicated. The infants, both boys, weighed 6 pounds and $1\frac{3}{4}$ ounces (2,771 Gm.) and 5 pounds and $12\frac{1}{4}$ ounces (2,615 Gm.). Both had undescended testicles, but otherwise appeared normal.

During the first few days the infants presented no abnormalities. On the fifth day the older one showed an excessive gain in weight and an edema of the lower part of the anterior abdominal wall. Two days later the second infant presented the same changes. The urinary bladder was then found distended in both infants, but there was constant though slight dribbling of urine. The bladder formed a globular mass reaching 1 cm. above the umbilicus. The edema extended gradually, involving eventually both the lower extremities and the face. Twitching of the upper extremities was noted on the seventh day. No obstruction was encountered when the infants were catheterized on the seventh day. The urine was clear and normal on chemical and microscopic examination. The catheterizations were repeated on subsequent occasions, and only twice did the catheter meet with some difficulty, but the bladder was entered each time. On the eleventh day of illness an exudate was found in the urine for the first time. The temperature, which had been normal or subnormal for the first eleven days, rose to 100.4 F. in the first child and to 101 F. in the second on the twelfth day after birth, or almost immediately after the exudate appeared in the urine.

There was a leukocytosis of 21,600 in the first baby and 18,200 in the second; 66 per cent were neutrophils and the others lymphocytes. The blood had a marked retention of nitrogenous substances: nonprotein nitrogen, 128 mg. per hundred cubic centimeters in the first child and 137 mg. in the second; urea nitrogen, 96 and 97 mg.; uric acid, 19.5 and 16 mg.; creatinine, 6 and 5.8 mg. The plasma chlorides were 500 mg. and 400 mg., respectively.

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From the Pathological Laboratories and the Obstetrical Department, Mount Sinai Hospital.

Roentgen examination of the spinal column showed no abnormalities. Skiodan was injected intravenously, but neither the kidneys nor the bladder was visualized.

The course was identical in both infants. The younger child died two days before the older one, on the seventeenth day. The clinical diagnosis was: genito-urinary abnormality and uremia.

The younger infant was examined eighteen hours after death. The body was well developed. Both testicles were in the inguinal canals. There was marked edema of the anterior abdominal wall, thighs and scrotum. The abdomen was markedly distended. The urinary bladder was 4 by 3.5 by 3 cm. The wall was greatly hypertrophied and 7 mm. thick. The mucosa was pale and moderately trabeculated. The lumen was filled with a cloudy, purulent urine. The ureteral orifices were patent. The posterior urethral orifice was markedly widened, and the dilated posterior urethra formed a continuation of the urinary bladder. The wall of the prostatic portion of the posterior urethra was hypertrophied and about 5 mm. thick. A probe was introduced into the posterior urethral orifice, but met with an obstruction after a short distance. When the same probe was introduced through

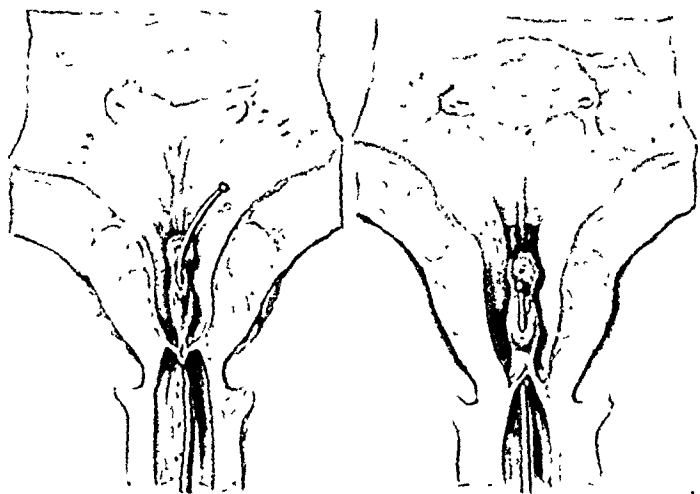


Fig. 1.—Drawing showing the trigon of the hypertrophied urinary bladder with the ureteral orifices, the posterior urethra, the enlarged colliculus seminalis, the utriculus and the valves, of each twin. Probes were introduced through the openings of the valves.

the anterior urethral orifice, it easily entered the urinary bladder. Water was introduced into the anterior urethral orifice by a syringe and cannula. It entered the urinary bladder in a continuous stream through the posterior urethral orifice. On reversal of the procedure, by introducing the cannula into the posterior orifice, no water appeared through the anterior orifice, even with considerable pressure. The urethra was then opened along its dorsal surface to the point of obstruction, which was due to a pair of mucosal valves extending from the anterior aspect of the enlarged and elevated colliculus seminalis (fig. 1). The valves extended distally on each side toward the lateral and anterior wall, and united at the top, thus encircling the entire circumference of the urethra and leaving as a communication a narrow slit in the center. In the fresh specimen the slit was hardly visible, but was readily demonstrable with a probe. In the hardened specimen the opening became exaggerated, owing to the presence of a probe during the process of hardening. The valves appeared ballooned out, with the convexity facing anteriorly.

The utriculus prostaticus and the openings of the ejaculatory ducts were present in their normal location on the colliculus seminalis. The urethra anterior to the valvular obstruction had no abnormalities. The testicles, prostate and seminal vesicles were unchanged. The ureters were tortuous, distended with a cloudy yellow fluid and 22 mm. in circumference (fig. 2). The right kidney weighed 45 Gm. It was soft and fluctuating. The capsule stripped with slight difficulty, owing to numerous subcapsular and parenchymal abscesses. On the surfaces made by cutting the normal structures were obscured by abscesses. The renal pelvis and the calices were dilated and distended with a thick purulent fluid. The mucous membrane was thickened and dull and had a few hemorrhages. The left kidney weighed 25 Gm. It presented changes similar to those in the right kidney, though not so advanced. The entire retroperitoneal space contained con-

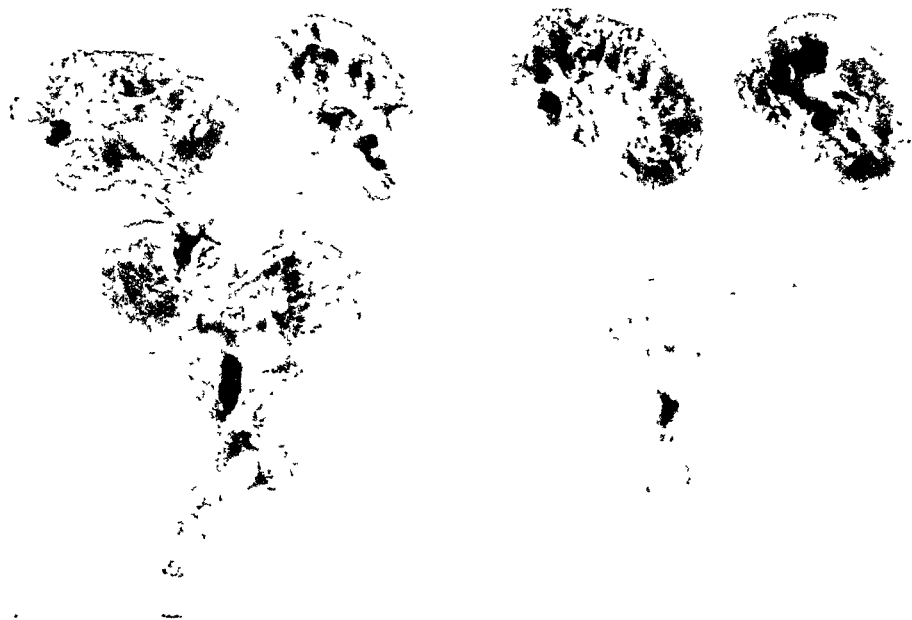


Fig. 2.—Photograph of the kidneys, ureters, urinary bladders and urethras of the twins, showing identical changes in both. The abscesses in the kidneys, the dilatation and tortuosity of the ureters and the hypertrophy of the urinary bladders are marked.

siderable quantities of a thick yellow exudate which surrounded the kidneys and suprarenal glands and extended to the diaphragm.

Histologic sections from the kidneys showed bacterial plugs in the tubular lumens as well as in the capillaries and arterioles. Smears and cultures from the urine and from the exudate in the kidneys and in the retroperitoneal space demonstrated *Staphylococcus albus*.

Numerous abscesses, ranging from 1 to 5 mm. in diameter, were found in the heart under the epicardium and endocardium and in both lungs. The other organs, including the brain, showed no significant changes. The anatomic diagnosis was: congenital valves of the posterior urethra, hypertrophy and dilatation of the prostatic urethra and the urinary bladder, acute ascending cysto-ureteropyelonephritis, pyonephrosis, acute suppurative perinephritis and pyemia.

In the body of the second infant there was a larger quantity of exudate in the retroperitoneal space. The kidneys were about 10 Gm. heavier on each side, and the ureters were somewhat less distended, but otherwise the changes were identical in every respect with those in first infant.

COMMENT

Various attempts have been made to classify valvular obstructions in the posterior urethra. The modern and popular classification by Young¹ considers three varieties: 1. One or two semilunar folds extending anteriorly from the verumontanum toward the penile urethra. 2. Such folds extending posteriorly from the upper edge of the verumontanum. This type is quite rare. 3. The iris valve, bearing no relation to the verumontanum, attached to the entire circumference of the urethra with a small opening near the center. This variety is extremely rare.

While it is generally agreed that the iris valves develop from persistent portions of the urogenital diaphragm, analogous to the anal and hymenal membranes, there is a great diversity of opinion as to the pathogenesis of the other two varieties. For a review of the different opinions, the reader is referred to the article of Kretschmer and Pierson.²

It is probable that there is a different developmental mechanism involved in the different types. The valvular obstructions which are included in the first and second group of Young have in common the convergence toward the colliculus seminalis. They seem best explained by the hypothesis of Lowsley,³ who suggested that the abnormal implantation of the wolffian and müllerian ducts into the posterior wall of the urogenital sinus may be instrumental in bringing them about. As a result of their normal implantation, they form an elevation on the floor of the prostatic portion of the urethra, the colliculus mülleri, which later becomes the colliculus seminalis or the verumontanum. The urethral crest, which is a continuation of the colliculus seminalis, bifurcates normally and forms very fine ridges running toward the lateral walls of the posterior urethra. In case of a lower implantation of the ducts, the colliculus, as well as the urethral crest, becomes more prominent. It is possible that occasionally the prominence of the crest and of its two arms may assume the proportions of mucosal folds which extend along from the posterior on the lateral, and eventually even on the anterior, wall of the urethra. The lateral or anterior insertion may end at any imaginable level, and in extreme cases a union may result, with the formation of a central slitlike opening of various

1. Young, Frontz and Baldwin: *J. Urol.* **3**:289, 1919.

2. Kretschmer, H. L., and Pierson, L. E.: *Am. J. Dis. Child.* **38**:804, 1929.

3. Lowsley: *Am. J. Anat.* **13**:299, 1912; *Ann. Surg.* **60**:733, 1914.

shapes and dimensions. In the further course the folds become exaggerated as a result of urinary pressure and assume the shape of valves.

The valves which run posteriorly from the colliculus seminalis toward the urinary bladder may be similarly explained as those running anteriorly, by the assumption that originally they also run anteriorly, but change their position as a result of the unequal growth of various portions of the posterior urethra, mainly in connection with the growth of the prostate. It is assumed that the posterior wall with the colliculus seminalis grows faster and is carried distally to a greater extent than is the roof of the urethra. Thus under certain, as yet undetermined, conditions the anterior course of the valvular folds may be reversed and directed toward the urinary bladder.

In connection with this hypothesis it is of interest that in all reports of cases with valves running anteriorly or posteriorly from the colliculus seminalis, the latter are reported as more or less markedly enlarged. Thus it appears that it would be justified to combine the two types of valves which Young classified as types I and II. We should like to suggest the term "pericollicular valves of the posterior urethra" for the combined type, and to subdivide the group into the anterior variety, which would correspond with Young's type I, and the posterior variety, which would be identical with type II. Such valves may be unilateral or bilateral.

The iris valves form a separate group, as do also the various forms of horizontal mucosal folds, proximally to or distally from the colliculus seminalis but not at all connected with it. The latter type may originate either from the posterior or from the anterior wall of the urethra, and is less known than the pericollicular variety. It is possible that these cases are more frequent than would appear from the reports in the literature, but rarely give rise to serious symptoms.

The particular interest in our two cases is due to the circumstance that the identical pericollicular valves were found in both twins. The question of the monozygotic or dizygotic nature of the twins cannot be answered because the placenta and membranes were not properly examined. The presence of the identical malformation in both twins can be construed with reasonable justification as favoring their monozygotism. DeLee⁴ stated that the same deformity often exists in monozygotic twins. He reported a case of double harelip, and quoted C. E. Black, who saw a pair of twins with a rudimentary colon.

4. DeLee, J. B.: *The Principles and Practice of Obstetrics*, Philadelphia, W. B. Saunders Company, 1924, p. 496.

CONCLUSION

Identical valves in the posterior urethra were found in twins. They produced an obstruction to the urinary flow, with the usual clinical and anatomic consequences. The clinical picture and the pathologic changes were identical in these twins. The term "pericollicular valves," with an anterior and a posterior subvariety, is suggested to replace types I and II of Young's classification. The modification is based on the apparent anatomic and suggestive embryologic relationships to the colliculus seminalis.

General Review

✓ HYPERPARATHYROIDISM (RECKLINGHAUSEN'S DISEASE OF BONE)

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INTRODUCTION

The Concept of Hyperparathyroidism: Its Evolution.—Von Recklinghausen, in 1891, fully described the changes in the bones in the disease entity (advanced stages) which has since been called generalized osteitis fibrosa cystica or Recklinghausen's disease.¹ He undertook, on anatomic grounds, to distinguish the condition from genuine osteomalacia. He succeeded, for the first time, in drawing a clearcut pathologic picture which definitely differentiated the advanced stage of this disease from osteomalacia. Von Recklinghausen clearly appreciated that cases 5 and 7 of his contribution to Virchow's Festschrift closely resembled those previously described by Engel² and by Langendorff and Mommsen.³ Each of these writers had reported a case of severe deforming osseous disease with cysts and giant cell areas, but they had erroneously interpreted the cases as instances of peculiar forms of osteomalacia. (Clinically, case 7 was considered as one of acute osteomalacia.) Hirschberg,⁴ in 1889, also reported a case which he misinterpreted as one of osteomalacia and which, from the description, was clearly one of Recklinghausen's disease. As Hirschberg's case was reported from Dresden (when the institute was under the directorship of Schmorl's predecessor), Schmorl⁵ had an opportunity to reexamine the pathologic material, and he recently recorded the fact that the bones undeniably showed generalized osteitis fibrosa cystica and not osteomalacia. It is interesting that more recently Denninger⁶ unearthed a skeleton which was estimated as being 1,000 years old, the gross appearance of which suggested that generalized osteitis fibrosa cystica had existed.

1. von Recklinghausen, F.: Festschrift Rudolf Virchow zu seinem 71. Geburtstage, Berlin, G. Reiner, 1891.

2. Engel, quoted by von Recklinghausen.¹

3. Langendorff, O., and Mommsen, J.: Virchows Arch. f. path. Anat. **69**:452, 1877.

4. Hirschberg, K.: Beitr. z. path. Anat. u. z. allg. Path. **6**:513, 1889.

5. Schmorl, G.: Virchows Arch. f. path. Anat. **283**:694, 1932.

6. Denninger, H. S.: Arch. Path. **11**:939, 1931.

In none of these early cases was any mention made of the condition of the parathyroid glands. It is readily understood why recognition of the parathyroid factor in Recklinghausen's disease came slowly, as these glands were not described as independent anatomic structures until 1880, while any part of their function remained in doubt until 1896. Vassale and Generali at that time, and others after them, showed that removal of the parathyroids—the thyroid gland being left intact—led to tetany. In 1909, MacCallum and Voegtlin⁷ and others established parathyroid insufficiency as the cause of this tetany, and found associated with it a fall in the serum calcium and a rise in the serum phosphorus. Greenwald and Gross⁸ further established that the total excretion of calcium was less after thyroparathyroidectomy than before.

While the syndrome of hypoparathyroidism (due to removal of the parathyroid glands) was first being investigated, the literature began to indicate that parathyroid enlargement may be found in certain diseases of bone. However, it was fully twenty years before a definite association was established between parathyroid enlargement and Recklinghausen's disease. The first indication in this direction came in 1904 from Askanazy,⁹ when he described, under the title "Ueber Ostitis Deformans ohne Osteoides Gewebe," his studies of the bones of a woman 51 years of age who suffered from multiple fractures. He believed that grossly the appearance of the bones suggested osteitis fibrosa rather than Paget's disease, but many of their features reminded him of the case of progressive bone atrophy which he had described in 1901.¹⁰ The pertinent finding in this case was that attached to the left thyroid lobe there was a tumor measuring 4.5 by 2 by 2 cm., which was composed of large cells suggesting suprarenal cortical cells. Askanazy stated that the tumor could have originated in the parathyroid gland. Although he did not specifically suggest a relationship between this apparent parathyroid tumor and the bone disease, in a later discussion of a paper by Weichselbaum¹¹ he made reference to this case and stated that such a relationship could be surmised. The choice of the title for Askanazy's report of 1904 is most unfortunate, as it creates the impression that the condition was Paget's disease—and this case is still frequently featured in the literature as one of Paget's disease associated with parathyroid adenoma.

It was, however, the classic anatomic and experimental investigations of Erdheim that conclusively focused the attention of pathologists

7. MacCallum, W. G., and Voegtlin, C.: *J. Exper. Med.* **11**:118, 1909.

8. Greenwald, I., and Gross, J.: *J. Biol. Chem.* **64**:185, 1925.

9. Askanazy, M.: *Arb. a. d. Geb. d. path. Anat. Inst. zu Tübingen* **4**:398, 1904.

10. Askanazy, M.: *Beiträge zur Knochenpathologie, Festschrift für M. Jaffé, Braunschweig, Vieweg und Sohn*, 1901.

11. Weichselbaum, A.: *Verhandl. d. deutsch. path. Gesellsch.* **10**:83, 1906.

on the possible relationship between abnormalities of the parathyroid glands and disease of bone. He discovered¹² that removal of these glands in rats leads to deficient calcification of the dentin of the incisors. This prompted him to investigate the condition of the parathyroid glands in his cases of osteomalacia.¹³ In a case described as one of puerperal osteomalacia, which he reported in 1907, he noted that one of the parathyroids was much enlarged (measuring 4.3 by 3.6 by 0.5 to 1 cm.), while the other three glands showed nothing striking, either grossly or histologically. A question arose in regard to the large gland in this case, as to whether the enlargement resulted from a compensatory hyperplasia or from formation of an adenoma. This is still a topic of much controversy in some phases of the subject of enlarged parathyroid glands. Erdheim inclined to the view that the enlargement was the result of compensatory hypertrophy secondary to the bone disease.

In his report of 1907, Erdheim presented seven additional cases of puerperal and senile osteomalacia, in which careful study of the parathyroids was made. In two cases, gross enlargement of one or more of the glands was found, with what he interpreted as microscopic evidences of hyperplasia. This he found in the enlarged as well as in the normal-sized glands. In the five other cases, no enlargement was apparent; however, in three of them he reported the presence of hyperplasia on histologic grounds. In a previous report he stated that fixing the parathyroids in Altmann's fluid and then treating them with osmic acid were technical details which should be followed in order to make certain of the presence of microscopic hyperplasia.¹⁴ More recently, Bergstrand¹⁵ contested the validity of this method in demonstrating hyperplasia microscopically. In this connection, mention may be made that disappearance of the interstitial fat cells from the parathyroid glands of adults is associated with hyperplasia of these glands, even without discernible gross enlargement.

Thereafter the literature was permeated with reports of enlargement of the parathyroid glands in association with diseases showing lesions of bone, such as Paget's disease, Recklinghausen's disease, osteomalacia, rickets and senile osteoporosis. Parathyroid enlargement was also reported in some cases of multiple myeloma, as well as in certain instances of carcinomatous metastases to the skeleton. In carefully controlled work on experimental rickets in rats, which related the

12. Erdheim, J.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **16**:632, 1906.

13. Erdheim, J.: *Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Kl., Wien* **116**:311, 1907.

14. Erdheim, J.: *Beitr. z. path. Anat. u. z. allg. Path.* **33**:158, 1903.

15. Bergstrand, H.: *Acta med. Scandinav* **54**:539, 1921.

rickets to a calcium-phosphorus imbalance with an added deficiency of vitamin D, parathyroid enlargement was likewise reported.

Furthermore, some degrees of parathyroid enlargement were also reported in a number of senile persons without bone disease. Other authors described enlarged parathyroids associated with paralysis agitans.¹⁶ MacCallum,¹⁷ as early as 1905, had observed a parathyroid gland measuring 2 cm. in a young patient with nephritis, who died of uremia; the bones were not investigated, but may have shown resorption. In addition, a number of reports appeared which indicated that considerable enlargement of a parathyroid was possible even without bone disease. Maresch's case¹⁸ may be taken as a perfect example; among others, he reported in detail a case of parathyroid tumor which measured 7 by 4 cm. by 13 to 17 mm.; the other three parathyroids were normal grossly and microscopically. The striking feature of this case was the lack of evidence in the bones of either active or healed disease. The large tumor was designated as an adenoma of the principal cells; in the capsule of the tumor a small normal parathyroid was seen.

It is plainly evident from the last paragraph that the state of knowledge concerning the relationship of parathyroid enlargement to bone disease soon became much involved. For a time, especially early in the development of the knowledge of this subject, the view more generally accepted was that originally postulated by Erdheim¹³ in regard to osteomalacia. He stated that the parathyroid enlargement should be looked on as the result of the bone disease rather than the cause of it; that is, the parathyroid enlargement was secondary. There can be no doubt that Erdheim was quite correct in his view regarding osteomalacia, which also holds for the enlargement of the parathyroid glands, if present, in a number of other conditions, such as multiple myeloma, carcinomatous metastases to the skeleton and rickets. But in time a number of observers began to question whether all parathyroid enlargements were secondary to the bone softening.

Thus, in 1915, Schlagenhauser,¹⁹ although not quite clear as to the distinctions between Recklinghausen's disease and genuine osteomalacia, suggested, on more or less empirical grounds, that it would be advantageous to attempt the removal of enlarged parathyroid glands in some of the malacic bone diseases. This was apparently the first definite deviation from the theory of compensatory hypertrophy.

16. Bergstrand.¹⁵ Harbitz, F.: *J. M. Research* **32**:361, 1915.

17. MacCallum, W. G.: *Bull. Johns Hopkins Hosp.* **16**:87, 1905.

18. Maresch, R.: *Frankfurt. Ztschr. f. Path.* **19**:159, 1916.

19. Schlagenhauser: *Wien. klin. Wchnschr.* **28**:1362, 1915; *Off. Protokoll, d. K. K. Ges. d. Aerzte, Wien., Sitzb. Dec. 3, 1915.*

In discussing Schlagenhauser's paper, Maresch stated that an investigation of the parathyroid glands in twenty-three cases of various malacic diseases of the skeleton revealed ten cases of genuine osteomalacia in which the parathyroids were slightly or not at all involved. In the instances of pronounced senile bone atrophy, the condition of the parathyroids was similar. Three of the twenty-three cases showed significant parathyroid enlargements. Two of these were undoubtedly instances of Recklinghausen's disease. Maresch, in this discussion, supported Schlagenhauser's suggestion that removal of the parathyroids should be attempted for therapeutic purposes in some of the malacic diseases.

In 1923, Dawson and Struthers,²⁰ reporting a case of generalized osteitis fibrosa with a principal cell adenoma of the parathyroid gland and extensive metastatic calcification of many organs and tissues, suggested that a cause and effect relationship may have existed between the adenoma and the bone changes. About this time literature on pathology contained several other reports in which this view was expressed.

The subject rested at this stage until about 1925, when several significant advances in parathyroid physiology were made. These were of utmost importance in finally clarifying the relationship between parathyroid enlargement and Recklinghausen's disease. At this time, the preparation by Hanson²¹ and Collip²² of active extracts of parathyroid glands²³ permitted experimental study of the effects of injection of the extracts. Furthermore, Mandl²⁴ discovered that removal of a parathyroid adenoma in generalized osteitis fibrosa cystica (Recklinghausen's disease) resulted in marked immediate clinical improvement of the patient, with diminution of the urinary excretion of calcium. Before reaching the happy conclusion in his case (that of a bed-ridden patient), Mandl, still under the influence of the Erdheim hypothesis of compensatory hyperplasia, had attempted homoplastic transplantation of the parathyroids, but this led to aggravation of the clinical symptoms. Thus, he was the first to give definite clinical proof that the bone changes in cases of osteitis fibrosa cystica were caused by a disturbed parathyroid function. Mandl's observations were soon confirmed and his conclusions widely accepted. A rapidly increasing series of reported cases, of which there are now about forty, have been brought forward to support the hypothesis of parathyroid hypersecretion. It is not my

20. Dawson, J. W., and Struthers, J. W.: *Edinburgh M. J.* **30**:421, 1923.

21. Hanson, A. M.: *Mil. Surgeon* **54**:76, 218 and 554, 1924.

22. Collip, J. B.: *J. Biol. Chem.* **63**:395, 1925; *Medicine* **5**:1, 1926.

23. The Collip extract is manufactured by Eli Lilly & Co. and sold under the trade name "parathormone."

24. Mandl, F.: *Arch. f. klin. Chir.* **143**:1 and 245, 1926; *Zentralbl. f. Chir.* **56**:1739, 1929.

purpose to consider separately each reported case; most of these contributions have been important in formulating a fuller conception of the various aspects of this disease.²⁵

The effects of the injection of parathyroid extract-Collip, especially in animals, were soon intensively investigated. It was shown that in susceptible animals, particularly dogs, small nontoxic doses raised the serum calcium and caused an increased excretion of calcium and phosphorus through the urine. Toxic doses of parathyroid extract raised the serum phosphorus in addition, caused urinary suppression, and rapidly led to the death of the animal. In time also, the effect of injection of parathyroid extract in man was investigated. Albright, Bauer, Ropes and Aub,²⁶ studying the effects of the administration of parathyroid extract-Collip on patients given an inadequate calcium diet, found a gradual increase of the urinary excretion of calcium but unaffected fecal excretion. The calcium level in the blood was gradually, but markedly, elevated. The extent of elevation of serum calcium varied in different persons, and was more marked when the patient was on a diet high in calcium. The injections of parathyroid extract also abruptly

25. It is finally of interest to mention here that a number of reported cases of osteomalacia with parathyroid adenoma have since been shown to have been cases of Recklinghausen's disease. Even such a master of bone pathology as Schmorl had permitted cases of Recklinghausen's disease to be reported from his institute by Hart (*Beitr. z. path. Anat. u. z. allg. Path.* **36**:353, 1904) and Molineus (*Arch. f. klin. Chir.* **101**:333, 1913) as instances of osteomalacia. Recently, Schmorl put himself on record as withdrawing their diagnoses of osteomalacia, stating that these cases were examples of Recklinghausen's disease.⁵ Molineus' three instances were reported in 1913, and each of the patients had a parathyroid adenoma. It is obvious from the foregoing statements that the literature still abounds in reports of cases purporting to be cases of osteomalacia which are palpably examples of Recklinghausen's disease. This is more especially so in cases in which cysts and giant cell tumors have been described with or without the presence of parathyroid adenomas.

In fact, it is possible that the first case in which there was an associated enlarged parathyroid gland reported by Erdheim¹³ in 1907 may have been one of Recklinghausen's disease rather than of osteomalacia. In this case the changes were most extensive in the pelvis, but only the calvarium, vertebrae and ribs were submitted to histologic examination. Erdheim stated that the marrow of the calvarium was very fibrous, while the osteoid borders of all the bones examined were very narrow; numerous osteoblasts were present. The very narrow osteoid borders, the fibrous marrow and the large numbers of osteoblasts would seem to militate against an absolute diagnosis of osteomalacia. It is true, this patient's condition was aggravated by pregnancy, and a diagnosis of puerperal osteomalacia seems supported by this fact. However, my colleagues and I have shown, in unpublished experiments with injections of parathyroid extract-Collip that severe lesions of hyperparathyroidism develop with smaller doses in pregnant guinea-pigs and rats than in nonpregnant animals; in fact, such animals usually die of acute hyperparathyroidism following doses that do not kill nonpregnant animals.

26. Albright, F.; Bauer, W.; Ropes, M., and Aub, J. C.: *J. Clin. Investigation* **7**:139, 1929.

increased the urinary excretion of phosphorus without affecting the fecal excretion. The phosphorus level in the blood was primarily lowered by parathyroid extract. With toxic effects of parathyroid extract the urinary phosphorus fell, and the serum phosphorus rose. Essentially, all these effects were observed earlier by Greenwald and Gross²⁷ in the metabolic studies with parathyroid extract-Collip which they carried out in dogs. In this connection, it is interesting to note the observation by Hannon, Shorr, McClellan and DuBois²⁸ that all the symptoms in their patient with Recklinghausen's disease were aggravated on injection of parathyroid extract-Collip.

Barr and Bulger,²⁹ recognizing the similarity between many of the clinical and chemical effects that result from the experimental injection of parathyroid extract-Collip in man and animals and the clinical and chemical features of Recklinghausen's disease, were the first to apply the term "hyperparathyroidism" to clinical Recklinghausen's disease.

Although extensive studies of the effects of acute and chronic experimental hyperparathyroidism were carried out after Collip's preparation of an active parathyroid extract, none of the investigators submitted the bones of their animals to complete examination. My colleagues and I,³⁰ between 1930 and 1932, were the first to report the effects of acute and chronic experimental hyperparathyroidism on the histologic appearance of the bones of animals. In addition, we reported certain chemical phases of our work.³¹ The studies were carried out on dogs, guinea-pigs and rabbits. The dog is most susceptible to the effects of hyperparathyroidism and readily shows changes in the bones and in the blood, while the rabbit is relatively very resistant to the effects of parathyroid extract-Collip. Therefore, the rabbit is not especially satisfactory for the pursuit of such studies.^{30e}

These experiments showed that many, if not all, of the pathologic changes observed in the bones in Recklinghausen's disease are produced in experimental hyperparathyroidism in susceptible animals. The studies brought to light irrefutable evidence that hyperparathyroidism was, in the main, responsible for the pathologic changes of Recklinghausen's disease. Thus the parathyroid enlargements—the adenomas—in association with Recklinghausen's disease were established as the direct cause of the bone changes.

27. Greenwald, I., and Gross, J.: *J. Biol. Chem.* **64**:217, 1925.

28. Hannon, R. R.; Shorr, E.; McClellan, W. S., and DuBois, E. F.: *Clin. Investigation* **8**:215, 1930.

29. Barr, D. P., and Bulger, H. A.: *Am. J. M. Sc.* **179**:449, 1930.

30. (a) Jaffe, H. L., and Bodansky, A.: *J. Exper. Med.* **52**:669, 1930. (b) Jaffe, H. L.; Bodansky, A., and Blair, J. E.; (c) *Arch. Path.* **11**:207, 1931; (d) *J. Exper. Med.* **55**:139, 1932; (e) *ibid.* **55**:695, 1932.

31. (a) Bodansky, A.; Blair, J. E., and Jaffe, H. L.: *J. Biol. Chem.* **88**:629, 1930. (b) Bodansky, A., and Jaffe, H. L.: *J. Exper. Med.* **53**:591, 1931; (c) *J. Biol. Chem.* **93**:543, 1931.

Some aspects of this work have since been confirmed by Johnson³² and by Abeloff and Sobel.³³ Rutishauser³⁴ stated that he produced considerable resorption and fibrosis of the bones of rabbits inoculated with mashed human parathyroid glands, obtained post mortem. In view of the marked resistance of rabbits to even huge doses of parathyroid extract-Collip, his results are surprising and would be important if confirmed. Johnson's results in experiments with dogs completely duplicate the findings reported by Bodansky and me. His experiments with rats show that rats suffering from severe hyperparathyroidism, after short periods of treatment, manifest all the histologic reactions seen by us following the injection of parathyroid extract-Collip in dogs and guinea-pigs. However, the roentgenograms and microscopic sections of the long tubular bones of the rats kept longest on parathyroid extract show plainly the development of a metaphyseal osteosclerosis which Johnson failed to discuss. It is interesting, in this connection, that Bauer, Aub and Albright³⁵ had noted grossly that in the growing rat the administration of parathyroid extract-Collip (885 units over a hundred and ten days), resulted in diminution of the length of the bones and in an increase of the number of trabeculae. My colleagues and I³⁶ have found that in rats which are fed on an edequate diet or one high in calcium (a diet which gives satisfactory growth of bone) and which are given injections of parathyroid extract-Collip over long periods of time, an extensive metaphyseal osteosclerosis develops which in many ways resembles the osteosclerosis following the ingestion of elementary phosphorus. This osteosclerosis is interpreted as a healing phenomenon associated with a compensation to the injection of parathyroid extract. We observed compensation to the prolonged injection of parathyroid extract-Collip in all species studied, but considered this problem specifically in relation to the guinea-pigs.^{36d}

Recently, Dr. David Shelling, of the department of pediatrics of Johns Hopkins Hospital, showed me a slide from a long tubular bone of a rat given parathyroid extract-Collip and fed on a diet high in calcium; this bone showed osteosclerosis. Selye,³⁷ in a recent paper, also observing the osteosclerosis induced by injection of parathyroid extract-Collip, attempted to correlate these changes with those of the marble bone disease described by Albers-Schönberg. He suggested that this disease might be due to a special form of hyperparathyroidism. I am firm in the belief that there is, in such experiments, no basis for asso-

32. Johnson, J. L.: *Am. J. M. Sc.* **183**:761 and 769, 1932.

33. Abeloff, A. J., and Sobel, I. P.: *Arch. Path.* **14**:471, 1932.

34. Rutishauser, E.: *Centralbl. f. allg. Path. u. path. Anat.* **53**:305, 1931-1932.

35. Bauer, W., Aub, J. C., and Albright, F.: *J. Exper. Med.* **49**:145, 1929.

36. Unpublished experiments.

37. Selye, H.: *Endocrinology* **16**:547, 1932.

ciating Albers-Schönberg disease with hyperparathyroidism. Selye ascribed the new bone formation in chronic hyperparathyroidism in rats to an osteoblastic stimulation induced by parathyroid extract-Collip. Our own experience, however, is that the new bone formation is a healing phenomenon in an animal that has compensated itself in adjustment to the state of hyperparathyroidism and in which bone resorption and new bone formation are still actively in progress.

GENERAL PATHOLOGY

Range of Changes in Bone.—Before entering into a description of the osseous changes of Recklinghausen's disease, it is advisable to point out that this disease is quite rare. Furthermore, it develops more or less progressively over a period of years, and certain important factors may enter to influence and modify the pathologic picture. These factors comprehend the age of the patient, the varying degrees of activity and secretion of the enlarged parathyroid, the character of the diet (acid or basic), the effects of complete or incomplete fracture, the duration of the disease prior to the study of the bones, the complications that conditions such as pregnancy would involve, etc.

The pathologic appearance of the osseous system may range from an advanced picture such as von Recklinghausen described, and to which the designation of generalized osteitis fibrosa cystica may rightfully be given, to one in which the lesions are so slight that they are almost indistinguishable grossly, such as that in the case described by Bergstrand.³⁸ In this case the bones showed microscopic evidences of active resorption, with numerous osteoclasts in somewhat enlarged haversian canals; there was an increase in connective tissue in these canals and about the bone trabeculae, but the major marrow cavities of the bones showed practically unchanged contents; there were no evidences of new bone formation, and cysts and giant cell tumors were absent. Furthermore, during life, the patient had many symptoms of hyperparathyroidism, and at autopsy two prune-sized parathyroid adenomas were found. Such cases may more rightfully be looked on as instances of progressive atrophy of bone or as cases of a form of osteoporosis caused by hyperparathyroidism.³⁹

38. Bergstrand, H.: Acta med. Scandinav. **76**:128, 1931.

39. Later it will be shown, on the basis of comparative clinical and experimental material, that what Askanazy,¹⁰ Pick (Berl. klin. Wchnschr. **54**:797, 1917), Schmorl (Verhandl. d. deutsch. path. Gesellsch. **21**:71, 1926) and Bodansky, Blair and I^{30c} have conceived of as progressive bone atrophy is the result of a progressive resorption and scarring of the bone with the prevailing of resorptive phenomena over the reparative reactions. The dissecting resorption of trabeculae is present both in advanced Recklinghausen's disease and in progressive bone atrophy, and is to be found especially in the spongiosa. Our experimental results on guinea-pigs show that all the features of progressive bone atrophy may be produced by chronic hyperparathyroidism.

When I state that hyperparathyroidism may produce the microscopic picture of osteoporosis, it is to be understood that I do not refer to the osteoporosis that occurs in senile atrophy or atrophy due to inactivity. In such conditions, the compact and the spongy bone become thin, but remain smooth. There is virtually no fibrous invasion of the haversian canals and the intertrabecular spaces. Rarely, some fibrous transformation occurs in association with senile atrophy and that due to inactivity, but it is never extensive. Thus, in designating Bergstrand's case as one of osteoporosis, the distinction is drawn between it and senile osteoporoses or those due to inactivity. This case is one of osteoporosis only in the sense that there had been resorption and some scarring of bone and marrow without transformation of its general architecture or much new bone formation. Hyperparathyroidism was plainly the initiating factor.

Between these two extreme types (generalized osteitis fibrosa with cysts and giant cell tumors, on the one hand, and progressive bone atrophy or osteoporosis on the other) are cases showing various degrees of implication and various stages of involvement of the different bones of the same patient. Thus, Dawson and Struthers'²⁰ case, in which many of the bones presented the classic evidences of Recklinghausen's disease (with cysts, giant cell tumors and extensive fibrosis of the major marrow cavity), showed no gross evidence of disease in the left femur. However, on microscopic examination, this bone displayed a very early stage of involvement. Microscopically, the haversian systems throughout the compacta were enlarged, while the trabeculae of the spongy bone were thin and the intertrabecular spaces were greatly widened; the normal fatty marrow within the major marrow cavity was practically unchanged. The enlarged haversian spaces of the compacta contained loose, vascular, fibrocellular tissue of varying amounts, with osteoclasts; they showed every transition in size from minimal enlargement to large irregularly contoured spaces. The entire middle third of the shaft cortex was undergoing this rarefaction, but nowhere on the walls of these canals was any new bone being deposited. Thus, in Dawson and Struthers' case, the changes in the left femur were in every respect identical with those existing in many bones in Bergstrand's case. The changes in the left femur are to be considered as incompletely advanced stages of the evolution of the disease; they help considerably in understanding many features of the pathogenesis of the disease picture.

On the other hand, in Schupp's⁴⁰ case there is shown a pathologic picture even further advanced than that described in the left femur in the case just cited. It is striking and important because no giant cell tumors or cysts were grossly present in any of the bones, although

40. Schupp, H.: *Deutsche Ztschr. f. Chir.* **233**:95, 1931.

there had been extensive resorption and transformation of the original bony architecture with new bone formation. The patient was a woman, 51 years of age, who gave a history of progressive weakness taking place over a period of five years. At autopsy there were found multiple fractures in the upper portion of the right femur, with transformation of the architecture of the skull, vertebrae, pelvis and other bones. Within the substance of the right thyroid lobe there was a parathyroid adenoma, measuring 1.5 by 0.5 by 0.75 cm., which, on histologic examination, was composed of principal cells. The bones showed resorption, with osteoclasts in Howship's lacunae, fine fibrous tissue transformation of the resorbed areas and deposition of lamellar osteoid bone with osteoblasts. As proof that the case was not one of osteomalacia, it is stated that osteoid borders were not present on the surfaces of any of the original bone seen in the sections.

No giant cell tumors were observed grossly or microscopically in any of the bones, although one pigmented area containing giant cells was found grossly in the body of the ninth dorsal vertebra, and nests of cells containing blood pigment were seen microscopically in other bones. Supported by his teacher, Schmorl, Schupp emphasized, as had others, that the presence of giant cell tumors and cysts is not essential in making a diagnosis of Recklinghausen's disease. However, in his own case he believed that fracture of the femur had occurred at the site of a former cyst, all vestiges of which had disappeared by the time the bone was studied at autopsy.

This is exactly the view that we have always held; some of our publications⁴¹ strongly emphasized this, even before Schupp's paper. In our work we stressed the belief that in experimental hyperparathyroidism, decalcification of bone is produced primarily. This may become pronounced and, with the consequent changes, may result in a pathologic picture that simulates the bone changes of clinical Recklinghausen's disease. The other features of the completed pathologic picture of chronic hyperparathyroidism in regard to the bone—that is, the proliferation of the marrow connective tissue, the numerous osteoclasts and Howship's lacunae, the appearance of new bone trabeculae in the connective tissue replacing the original bone, the marrow hemorrhage and giant cell tumor formation, the numerous small and some large cysts and even fractures—are wholly dependent on and consequent on such decalcification. This is also true of any healing phenomena.

By indicating that primary decalcification is the condition on which all the subsequent changes are superimposed, we do not imply that an appreciable interval of time exists between the decalcification and the appearance of any secondary phenomena. Furthermore, while many features other than initial decalcification were enumerated for the

41. Jaffe and Bodansky.^{30a} Jaffe, Bodansky and Blair.^{30c}

entire osseous picture of chronic experimental hyperparathyroidism, certain of them are more important and appear quite regularly with the progressive decalcification. These are the appearance of osteoclasts and Howship's lacunae and the proliferation of the marrow connective tissue. Others occur less constantly, occur in varying degrees, and are much more dependent on complications for their manifestation—these are giant cell masses following marrow hemorrhage and cysts.

From the foregoing facts one deduces that most of the essential features of the pathologic changes in the bones in cases of clinical hyperparathyroidism are secondary to a rapid decalcification of the skeleton, induced by the hypersecreting parathyroid adenoma or adenomas. The final pathologic picture is modified by, and varies with, the age of the patient, the duration of the disease, the intake and availability of mineral salts, the speed and degree of decalcification and the stresses, strains and possible injuries to which the decalcified skeleton is subjected. It seems fair to conclude, then, that investigators are becoming fully aware of the all-inclusive range of the pathologic changes of hyperparathyroidism. With this knowledge as a starting point (and with the additional accumulating evidence that removal of the hypersecreting parathyroid tissue causes interruption of the course of the disease and often permits considerable healing), there is a real prospect that the severe deforming processes, such as were originally described by von Recklinghausen, will disappear completely because of early diagnosis. One is encouraged in this view by the fact that the chemical changes produced in the body by parathyroid hyperactivity can be detected by chemical study of the blood and of the excretions of such patients and clinical diagnosis thereby greatly aided.

Distribution of Changes in Bone.—In von Recklinghausen's case 7 (a very advanced case), while the disease to some degree involved practically the entire skeleton, the changes were most pronounced in certain bones and bony parts. The long tubular bones showed the greatest degree of change and transformation (closely followed by the spine, including the sacrum, pelvis, skull, jawbones and thoracic flat bones). On the other hand, the short tubular bones, such as the metatarsal and the basal and middle phalanges, showed only the mildest degrees of transformation. The tarsal bones were even less transformed; they were highly porotic, the trabeculae being extremely thin and the intertrabecular marrow quite fatty.

With regard to the long tubular bone, the greatest amount of transformation and new bone formation, in a very advanced case, is usually found in the diaphysis. In von Recklinghausen's case, the extreme ends of both tibias and the lower end of the right femur showed limitation of the disease to the region near the former epiphyseal-diaphyseal junctions. The portions near the articular cartilages were only greatly

porous, the cancellous spaces still containing fatty marrow. In bones which were very extensively diseased, such as the radii, fibulae, left humerus and upper portion of the right femur, the spongy trabeculae of the ends of the bone beneath the articular cartilages were of more or less normal texture. Von Recklinghausen stated that the relative freedom of the epiphyseal ends from involvement by fibro-osteoid tissue was especially noticeable in the metatarsal and phalangeal bones, in which the disease was practically limited to the cortex, while the marrow cavity contained the normal fatty marrow.

It is interesting that when Bodansky, Blair and I⁴² made a survey of bone lesions appearing in experimental chronic hyperparathyroidism, we found that the severity and the distribution of these lesions followed, to a great degree, the same pattern of involvement as indicated in the advanced clinical case just cited. The striking feature of this similarity in distribution is that von Recklinghausen's patient was an adult, while the experimental studies were carried on in young, growing animals.

In an attempt to understand such localization, we made a study of the embryogenesis and postnatal development of the skeleton. Our analysis indicated that the most pronounced resorption of bone in experimental hyperparathyroidism occurs in certain sites of predilection, and that the greater susceptibility of these sites may be related to their rate of bone formation. We found that the tarsal and carpal bones and the epiphyses of young guinea-pigs are sites of relatively slow growth. The general principle that we propounded was that the sites of most active bone formation are the sites most susceptible to resorption. Thus, the portions of the skeleton most susceptible to decalcification are those in which formation of bone is most active.

The pronounced susceptibility to resorption (as a result of hyperparathyroidism) of the spongy bone of the metaphyses thus becomes intelligible, especially the spongy bone of the metaphyses of the rapidly growing long tubular bones, of the costochondral junctions, of the cortices of the shafts, particularly near the former epiphyseal cartilage plates, of the cortices of the ribs used most in the respiratory act and of the bones of the skull and lower jaw. This conception offers an explanation as to why the metaphyses of the slower growing short tubular bones showed relatively little evidence of resorption, while the cortices of the shafts of these bones showed practically no evidence of resorption. At the same time, the spongy bone of all epiphyses and of the tarsal and carpal bones, when subjected to conditions producing the lesions described, showed at the most only generalized thinning.

Furthermore, this conception clarifies the greater susceptibility to parathyroid extract noted in the skeletons of actively growing young guinea-pigs compared with the skeletons of adult guinea-pigs. It also

42. Jaffe, H. L.; Bodansky, A. and Blair, J. E.. Arch. Path. **12**:715, 1931.

explains the quantitative differences in the response of different bones and of different portions of given bones in animals treated with parathyroid extract. These differences are observed strikingly in young animals, but also to a certain degree in older ones.

The quantitative relation of resorption of bone to the rate of growth in particular sites may be further extended to include endosteal and periosteal resorption. In young, rapidly growing animals, with the shafts of tubular bones increasing in diameter, the marked degree of subperiosteal resorption that is observed in experimental hyperparathyroidism corresponds to the rapid growth in the subperiosteal regions in the normal animal. In the older animal, in which, normally, subperiosteal growth is greatly diminished, subperiosteal resorption is correspondingly less marked, while subendosteal resorption becomes by far the more prominent factor.

Thus, on the basis of our experimental work we have been able to show that in hyperparathyroidism there is a greater tendency for certain bones to be involved than others; and, finally, that those bones which show a great tendency toward involvement evidence the severest involvements in certain sites of predilection. In addition, it must be considered that in both experimental and clinical hyperparathyroidism an apparent discrepancy in the degree of involvement may exist between two bones (such as the femora) which, on the basis of the conception stated, should be equally involved. The difference may logically be attributed to the association of complicating factors, such as infractions or fractures, or the favoring of bones that would result in more pronounced disease of the bones of the unfavored extremity.

SPECIFIC PATHOLOGY

Appearance of a Long Tubular Bone With Advanced Disease.—In any specific case of Recklinghausen's disease, many bones may be extensively diseased, or a few bones may be greatly diseased while others disclose evidences of only microscopic involvement; finally, there are cases in which the bony lesions are discovered only by the aid of the microscope. It is manifestly impossible to describe minutely each degree of pathologic change to which the bones may be subjected in this disease. The description must be limited to certain degrees of gross variation.

When an extensively involved long tubular bone is examined, the transverse diameter is usually found expanded at some point, sometimes in several places. If the bone is the femur, a considerable degree of coxa vara may be present. The details of the gross appearance may be modified by the presence of recent or healed fractures which create local deformities or very extensive deformation of the bone. The deformation may be so pronounced as to result in a snakelike form similar

to that described in the older publications on osteomalacia. The periosteum surrounding a bone with such an advanced lesion is usually thin; it participates in the general atrophy of tissue that occurs in this disease. If there is any periosteal reaction—which is rare—it is likely to be found in the vicinity of fractures or in regions in which the bone needs reinforcement because of the presence of a cyst or giant cell tumor that is insidiously undermining the integral structure of the bone (the subperiosteal new bone formation being an effort at repair or strengthening). However, even with the expansion of bone attendant on the presence of cysts or giant cell tumors, the overlying periosteum is most likely to evince no reaction.

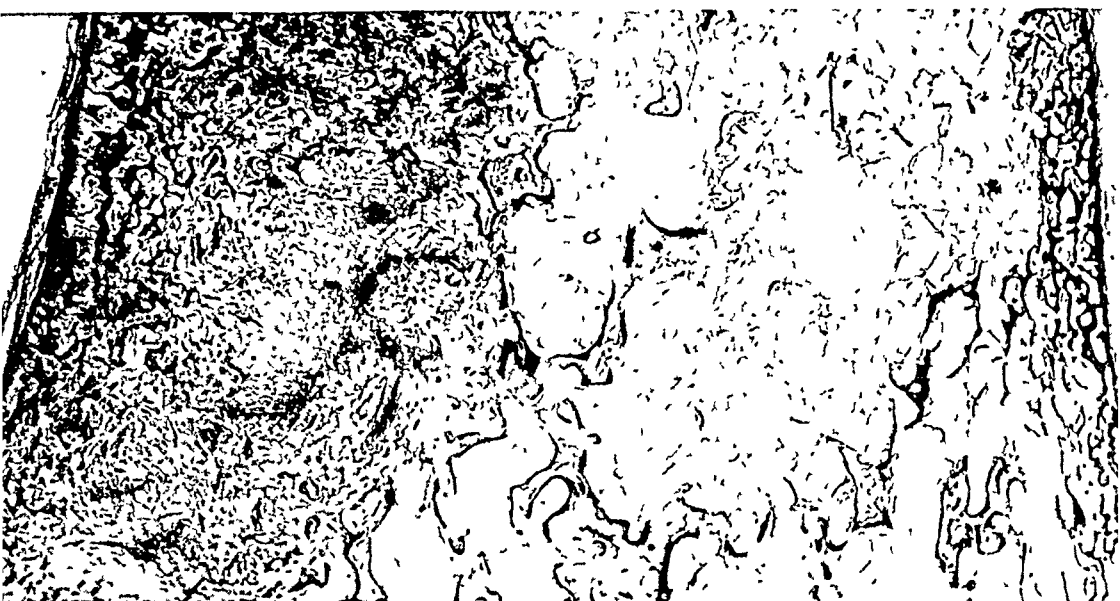


Fig. 1—A longitudinal section through the diaphysis of a long tubular bone; the periosteum is thin; the major medullary cavity shows a fibrous focus on the left, in which newly formed bone is evident; the rest of the marrow is fatty (right); the original cortex on the right is thin, owing to marked resorption, on the left it is to a considerable degree replaced by the fibrous focus; $\times 4$.

Longitudinal section (a severely involved bone may even be cut with a knife) will disclose almost a complete change from the normal structure of the bone (fig. 1). The major medullary cavity may show considerable replacement of the original tissue by scattered, grayish-white, fibrous foci in which finely reticulated bone may be felt. The marrow cavity may be traversed by single and multilocular cystic spaces which can extend beneath the periosteum. In and between such cystic spaces, recent and old hemorrhage may be present, as well as brownish discolored areas (giant cell tumors). Other areas of the marrow may be fatty or myeloid. In the extreme upper and lower ends of such a

bone, the spongiosa and the intervening cancellous marrow usually manifest the least amount of pathologic deviation; in such areas the bony trabeculae are extremely atrophic. The intertrabecular marrow is fatty; fibrous foci such as are seen in the diaphysis are usually absent. However, immediately beneath the articular cartilage, a slight amount of marrow fibrosis and new bone formation may sometimes be observed; that is, the subchondral spongiosa may be converted into a fine spongy condensed mass of new bone.¹ When the subchondral changes are not

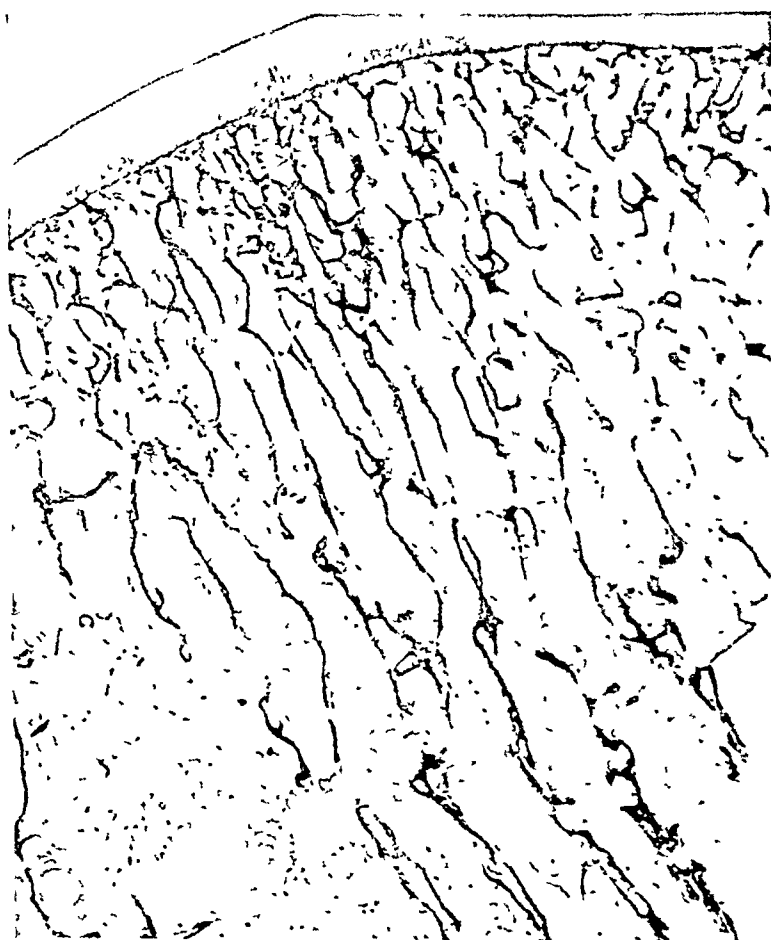


Fig. 2—The extreme (epiphyseal) end of a long tubular bone; the bony trabeculae are extremely atrophic; the intertrabecular marrow is fatty; $\times 4$.

43 Such subchondral conversion is frequently observed in the bodies of the vertebrae where the spongiosa immediately beneath the usually expanded intervertebral disks is likely to be more or less uniformly condensed. The subchondral spongiosa in the bodies of the vertebrae in Recklinghausen's disease is strikingly different from that observed in Paget's disease. In the latter, the new, spongy trabeculae (of affected bone) are irregularly placed and thickened, closely set or widely separated. They are never as regularly condensed as in Recklinghausen's disease (fig. 5).

obvious grossly, microscopic examination may still reveal the presence of small amounts of fibrous marrow and collections of giant cells in the vicinity of the bony end-plate, sometimes with its complete destruction. Under such circumstances, fibrous tissue, giant cells and newly formed bone may extend into the articular cartilage. The articular cartilage is entirely passive in this disease (figs. 2 and 3).

The original cortex may undergo tremendous change—even to the extent of being completely replaced. Whatever may remain of the original cortex is always thin, owing to marked resorption. It shows a very porous structure, and the resorption may advance to such a pro-



Fig. 3.—A higher power magnification of area shown in figure 2. The subchondral spongiosa reveals microscopically the presence of small amounts of fibrous marrow in the vicinity of the bony end-plate; there is slight new bone formation on a resorbed trabeculae; $\times 125$.

nounced degree that only a thin layer of bone denotes its presence. As the resorption and transformation of the cortex proceed, newly formed bone is deposited. The fibrous foci within the medullary cavity containing the reticulated bone merge in places with the newly formed cortical bone so that the demarcation between cortex and medulla may be completely obliterated.

It is to be noted that the pathologic appearance of such a bone has resulted from a transformation of most of the original bony architecture, with its replacement by large amounts of fibrous tissue in which

poorly calcified new bone forms. In addition, whatever original bone remains has become markedly atrophic.

On microscopic examination, the appearance of connective tissue fiber bone in the fibrous foci within the medullary cavity may be observed. The final conversion of some of these newly formed bony trabeculae into rather immature lamellar bone may also be traced. The new bone formation is the result of metaplasia of osteoblastic connective tissue into bone. The trabeculae of the newly formed fiber bone fuse to produce a reticulum on which lamellar bone formation proceeds as in endochondral ossification. In Recklinghausen's disease there is a great tendency toward the rapid resorption of this newly formed bone; therefore numerous osteoclasts are observed in lacunae on the surfaces of such bone trabeculae or about small fragments of excessively resorbed trabeculae. Furthermore, large areas of connective tissue formation in which no bone appears may also be seen. In such fibrous foci, which are often present subperiosteally, multinucleated giant cells and considerable extravasated blood may appear. The cellular elements within such foci can be quite varied.

On histologic examination, osteoclasts are to be found in abundance during all active stages of the evolution of the pathologic process. During the resorption of the original bone, they are to be found on the surfaces of the enlarged haversian canals and the surfaces of the trabeculae, both periosteally and subperiosteally. They are, of course, found in association with Howship's lacunae. As the original bone is being replaced, the new bone appears in the connective tissue; the removal and the rebuilding of this new bone are also associated with numerous osteoclasts. In our experimental work, we found that the emphasis which the older pathologists laid on osteoclasts as a special feature of the pathologic picture of generalized osteitis fibrosa cystica was justified. In the experimental condition, the appearance of great numbers of osteoclasts is a particular feature in relation to the decalcification and resorption of the original bone and of the newly formed connective tissue bone.

It is striking that in this disease the tendency to resorption and decalcification by far exceeds the tendency to new bone formation. This is explained by the constant drain on the calcium reserves to which a patient or animal suffering from chronic hyperparathyroidism is subjected. The predominance of the process of resorption over new bone formation is one of the features of Recklinghausen's disease which distinguish its microscopic picture from that of Paget's disease. As previously indicated, the appearance of osteosclerosis in rats on an adequate calcium diet, given injections of parathyroid extract over a long period, is evidence of healing in association with continued resorption.

While it is true that areas of a bone with Paget's disease may present a histologic appearance indistinguishable from that of Recklinghausen's disease, in most areas of Paget's disease new bone formation outruns resorption. Thus, there is little reason for confusion between them. The newly formed bone of Paget's disease takes on a distinguishing microscopic picture, owing to the numerous thick, irregular and dark-staining cement lines, which give the bone the appearance of an irregular mosaic—a feature to which others have alluded, but to which Schmorl⁵ ascribed diagnostic significance.

In Recklinghausen's disease, such an irregular mosaic architecture is rarely to be observed except possibly in the skull, if it is thickened. When, in certain regions, deposition of new bone can be maintained in excess of resorption, cement lines appear, but these are never as irregular, as numerous or as thick as those in Paget's disease. Thus, the irregular mosaic-like appearance, so prominent in the microscopic picture of Paget's disease, is not created in Recklinghausen's disease.

In chronic experimental hyperparathyroidism we did not find the irregular mosaic structure. In the bones of young guinea-pigs receiving intermittent injections of parathyroid extract-Collip a large number of new cement lines resulted. These were, however, fairly regularly disposed. They were indicative of the periodic decalcifications and restorations to which these bones were subjected during the long course of intermittent chronic hyperparathyroidism.^{30d}

Although new bone formation is not excessive, it may be observed in both clinical and experimental hyperparathyroidism. Even while original cortical bone is being resorbed and the canals of its blood vessels are being widened, a low power survey of such a cortex will show the deposition of narrow margins of newly formed bone covered by osteoblasts on the walls of the enlarged canals. These osteoid margins are in no way comparable to the thick osteoid borders observed in osteomalacia and in rickets. It is one of the peculiarities of bone as a tissue that, in spite of the existence of conditions causing its resorption and depletion, a tendency exists to counteract the resorptive forces by new bone formation.

The advanced stages of Recklinghausen's disease are frequently associated with brown lesions of the bones, composed of giant cell masses. These are generally designated as giant cell tumor areas. However, a bone may become extensively diseased without the appearance of such giant cell tumors, even microscopically. When present, their number and size vary greatly in different cases. Some are minute, whereas others are large enough to expand part or all of the circumference of a long tubular bone. The largest have been known to reach the size of a child's head. If revealed only on microscopic examination, they appear as nests of giant cells in a cellular, fine-fibered marrow, which also contains numerous granules of blood pigment (microscopic

brown tumors). They are most likely to be present in the metaphyses, and fractures frequently occur at their sites if they reach a large size. Their presence in any region of a bone denotes marked progress of the pathologic process.

Histologically, these brown giant cell masses are composed of a spindle cell connective tissue stroma which seems to be continuous with the ordinary outlying connective tissue stroma. The giant cells, which may be so numerous as to overshadow the supporting stroma completely, are identical with the osteoclasts; they have phagocytic activities and often contain changed red corpuscles or hemosiderin. Frequently the number of giant cells is relatively small. The brown color of these tumors is apparently dependent on hemorrhage, the color being the result of blood pigment within phagocytes in the fibrous connective tissue.

Healing processes may be observed in brown tumors; they take place through conversion of the affected area into a cell-poor, sclerotic connective tissue, which may even become partly calcified. Collections of giant cells under such circumstances may remain in the peripheral zones. It is possible that these lesions may even disappear spontaneously. Large giant cell areas may eventually become cystic, with little of the original tissue remaining; cyst formation is also considered as evidence of spontaneous healing. In cases of Recklinghausen's disease in which parathyroid adenomas were removed, giant cell areas observed roentgenologically have been reported as disappearing.

The mode of origin and the significance of the giant cell masses have been debated since von Recklinghausen's time. One question seems definitely settled: that is, they are not genuine tumors or blastomas. Whether they are to be considered as a special type of inflammatory or reactive new bone formation, in consequence of hemorrhage that has occurred in fibrosed marrow, cannot be decided now. This view, however, seems to be the most acceptable one at present.

There has been active discussion as to whether the periosteal and the central epulides of the jaw (which may occur without hyperparathyroidism) are to be differentiated pathogenically from the brown tumor masses of Recklinghausen's disease.⁴⁴ It seems fair to assume that since the epulides and the solitary giant cell tumors (which occur especially in the epiphyses) frequently have the characteristics of blastomas, they are to be separated from the brown tumors of Recklinghausen's disease, which resemble them only histologically. Pick,⁴⁵ among others, recently expressed himself in favor of this point of view.

There is also considerable variability among the cysts. They may be quite numerous; they may be absent entirely; sometimes they are

44. Hellner, H.: *Arch. f. klin. Chir.* **165**:229, 1931.

45. Pick, L.: *Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffwechselkr.* X. Tag. Budapest, 1930, Leipzig, G. Thieme, 1931, p. 146.

recognized only microscopically. When they are present and recognizable grossly, the involved bone may contain but few, or it may show them in such multiplicity as to give the appearance of generalized cystic degeneration. The cysts occur most frequently in the larger areas of fibrous marrow and are located within the metaphyses or diaphysis. They may expand the shaft of a bone and be the underlying cause of fracture. At other times, cysts may extend to the periosteum, being separated from it by a thin fibrous layer of tissue and a shell of bone.

The larger cysts are unilocular or multilocular. When they are multilocular, the dividing septums are fibrous tissue walls within which



Fig. 4.—A long tubular bone showing cysts and a giant cell tumor area; the brown lesion is observed in the upper left portion of the photomicrograph; several large cysts and a number of smaller cysts are also observed; newly formed bone is seen about the cysts on the left; $\times 4$.

thin trabeculae of bone may be found. These larger cysts may be lined by a condensed layer of fibrous tissue, beneath which newly formed bone may be present; in others the wall is less well defined. Coagula of thin albuminous material can often be found in the larger cysts; such coagula may be admixed with red blood cells, phagocytic cells and sometimes cholesterol crystals. Some of the cysts contain large amounts of blood and fibrinous clots, while others may be empty. The intercystic tissue is frequently fibrous tissue, with or without hemorrhage, and new bone in various stages of formation is also observed between the cysts (fig. 4).

There has been much conjecture concerning the possible modes of origin of cysts, particularly of the larger ones. It seems fair to assume that they may arise in several ways. Some of them certainly have had their beginning as a result of edema and degeneration of the fibrous marrow, as microscopic examination reveals spaces in the meshes of the edematous fibrous tissue. These spaces may enlarge and fuse, the intervening septums undergoing degeneration, with the formation of larger cysts. Hemorrhage, through the rupture of vessels, may be a contributory factor in altering their appearance and content. Cysts may also result from degenerations occurring within giant cell tumor areas; large cystic spaces filled with thin, blood-stained fluid appear as a result. In addition to the larger cysts, the connective tissue (in the porous cortex and between the newly formed trabeculae of bone in the fibrous marrow) contains a great abundance of small dilated, cystlike blood and lymph channels. These dilated spaces arise through stasis. Cysts of this type were seen in our animals suffering from chronic hyperparathyroidism.

A long tubular bone showing the advanced pathologic changes of generalized osteitis fibrosa cystica may show evidences of recent or healed fractures. Such bones break with the slightest trauma and frequently such a fracture may be the first serious clinical feature to draw attention to the disease. Fractures are much more common in Recklinghausen's disease than in Paget's disease. The resultant deformities may be worse even than those observed in osteomalacia. It is surprising that in spite of the sluggishness of the periosteum in proliferating, fractures heal fairly readily, although refractures may occur.

Advanced Pathologic Changes in Other Bones.—The foregoing description of the pathologic changes in a long tubular bone much involved by the disease may apply to any long tubular bone in the body. Essentially the same pathologic changes are present in any other bone markedly involved.

The vertebral column may be deformed, showing kyphosis or scoliosis or both. In advanced cases, a really continuous subperiosteal bone layer may be absent. Owing to the marked decalcification of the bodies, the turgid intervertebral disks become expanded and discoid, with resultant reduction in the superior-inferior diameter, especially through the center of many bodies. Thus, the fishlike spine appears. (Such appearances are manifested in other conditions also, especially in senile osteoporosis.) Beneath the expanded intervertebral disks there is usually a considerable layer of newly formed trabeculae of finely condensed bone. Between these trabeculae there is a vast increase of fibrous tissue, and numerous osteoclasts are to be observed on the sur-

faces of such trabeculae. Within the deeper substance of the body, a great amount of atrophy of the original trabeculae occurs; there is likewise a great amount of marrow hemorrhage; there may be cystic spaces and giant cell tumors. The normal lymphoid marrow may also persist if the fibrous transformation is not too extensive (fig. 5).

The deformity of the vertebral column, together with the changes in the ribs and sternum, may result in a badly misshapen thoracic cage. The ribs can become extremely atrophic, and some, especially the lower ones, may assume irregular shapes and impinge on the iliac crests.



Fig. 5.—A longitudinal section of a vertebral body is shown; beneath the intervertebral disk, considerable newly formed trabeculae of finely condensed bone are seen; the other trabeculae are atrophic, and marrow hemorrhage is present; cortical defect of the body is observed on the right; $\times 4$.

Calluses at the sites of healed fractures are frequently observed, while the ribs may show cortical expansion owing to the presence of cysts and giant cell tumors.

Deformity of the pelvic bones also results. The brim becomes extremely asymmetrical and distorted and much reduced in size. The distortion in the shape of the pelvis may approximate the type of deformity observed in advanced cases of puerperal osteomalacia. This is one of the reasons why advanced generalized osteitis fibrosa cystica has been confused with osteomalacia. The iliac bones are likely to become

expanded; when they are replaced by pathologic new bone, they are easily compressible and flexible.

The short tubular bones may show pronounced changes with cysts and giant cell tumors, though they are less likely to present as marked degrees of implication as long tubular bones. The tarsal and carpal bones may be atrophic, with no other involvement.

The bones of the calvarium may be thin, atrophic and quite pliable; the thinning may proceed to such degree that bony defects are present. On the other hand, but not as often, the calvarium may be thickened, in many ways, especially roentgenologically, suggesting the appearance of the skull in Paget's disease. Thickening of the skull in certain cases of generalized osteitis fibrosa cystica was one of the reasons why this disease and Paget's disease were closely linked as different manifestations of a common basic disturbance. This theory, in view of the present knowledge of hyperparathyroidism, is now definitely discredited. Why the skull thickens in certain cases of Recklinghausen's disease is not known.

The thinned calvarium, from which the pericranium is stripped, presents a rough, vascular-looking surface; the sutures are obliterated; the calvarium may easily be cut with a knife. The cut surface shows disappearance of the normal division into inner and outer tables with intervening diploe. The bone that has replaced the normal components is made up of intertwining new-formed trabeculae. They have a more or less parallel arrangement immediately under a poorly cellular periosteum. The outer trabeculae are coarse-fibered and contain calcium; deeper, the trabeculae are irregular and show less calcium on staining. The same relationship holds from the dural surface outward. The intertrabecular spaces are filled with connective tissue, and this tissue becomes more or less continuous with the periosteum on the outer surface and the dura on the inner surface. Osteoclasts are seen in large numbers on the surface of original bone and also on the new bone that is being transformed. In some areas large fibrous foci without any new-formed bony trabeculae are to be observed, within which some scattered osteoclasts may be found.

A calvarium that is thickened is usually not uniform in this change. The region most thickened may measure as much as 2 cm. or even more. The cut surface in such an area is finely porous and usually injected. The sutures, as in the thin calvarium, are obliterated, and the vascular grooves may be quite deep. The histologic appearance of a thickened zone is that of complete replacement of the normal architecture by slender trabeculae which are most regularly arranged externally and internally; the trabeculae between the inner and outer layers are irregular in shape and form a close-meshed spongiosa. The marrow is fibrous

throughout. The cement lines may be fairly numerous, but they never reach, either in number or in irregularity, the proportions they do in Paget's disease.

Progressive Atrophy of Bone: Early Stage of the Disease.—In the early stages of the evolution of Recklinghausen's disease, the pathologic picture of the skeleton is in every way comparable to the pathologic picture of the condition described by Askanazy¹⁰ in 1901 as "progressive bone atrophy."⁴⁶ Askanazy,⁴⁷ in 1932, discussing progressive atrophy of bone, attempted to establish for it a distinct and separate place in the pathology of bone. He would not definitely admit that progressive atrophy is an early stage of generalized osteitis fibrosa cystica, holding that the distinguishing feature of the microscopic picture in this condition is the absence of new bone formation. A case of Recklinghausen's disease described by Bergstrand,⁴⁸ in which there were only very mild changes in the bones disputes this point of view. Two pruned parathyroid adenomas were found at autopsy. The bones showed active resorption, but there was no evidence of new bone formation.

There can be no doubt that the histologic picture of progressive atrophy of bone appears under a number of circumstances, in man and in animals. From these examples the inference may be made that the pathologic picture of progressive atrophy of bone is not one that is specifically related to any single etiologic factor. In this connection, Schmorl⁴⁸ stated that the pathologic changes of progressive atrophy of bone with its dissecting resorption may without any question be observed in Recklinghausen's disease. In four cases showing progressive atrophy of bone he found parathyroid tumors, and in three of these, multiple giant cell tumors were also present; metastatic calcification was not observed in any of them. In all four cases Schmorl described dissecting

46. His patient, a woman 54 years of age, died of suppurative peritonitis following rupture of the pelvis of a kidney by a renal stone. At autopsy he found metastatic calcification of the stomach, lung and kidneys. Gross examination of the spine and sacrum gave him the impression of a mild osteoporosis; microscopically, he found in all sections that the bony trabeculae were markedly resorbed, and from 40 to 80 osteoclasts were present in each field. The bony trabeculae were pierced through by newly formed connective tissue tracts, while, on the whole, the intertrabecular marrow was not fibrosed. This peculiar dissection of the trabeculae has come to be called, in the pathology of bone, "dissecting resorption." The surfaces of the original trabeculae also showed increased connective tissue and osteoclasts. Bony deformity was not present. In the mediastinum there was a necrotic calcified tumor mass which Askanazy designated as a thyroid carcinoma, difficult to differentiate microscopically from a parastruma. He speculated on the relation of this tumor to the bone lesion.

47. Askanazy, M.: Schweiz. med. Jahrb., Basel, B. Schwarz & Co., 1932, p. CVII.

48. Schmorl, G.: Verhandl. d. deutsch. path. Gesellsch. **21**:71, 1926.

resorption in the spongiosa of the vertebrae. Dissecting resorption is characterized microscopically by the perforation or dissection of original bony trabeculae by tracts of connective tissue (fig. 6). Furthermore, such trabeculae also show resorption on their surfaces. If new bone is deposited on the surfaces of trabeculae undergoing dissecting resorption, it is never profuse; such depositions are arranged in parallel formation. Dissecting resorption is not observed in Paget's disease.

In chronic experimental hyperparathyroidism in guinea-pigs, Bodansky, Blair and I^{30c} found that the lesions in the bones corresponded more with those of progressive atrophy of bone (as described by Askanazy in man and by Lévy⁴⁹ and Pick⁵⁰ in rodents) than with those more regularly found in Recklinghausen's disease. Lévy described an adult tuberculous rabbit in which metastatic calcification of the soft



Fig. 6.—Dissecting resorption of trabeculae at the (epiphyseal) end of a long tubular bone; there is dissection or perforation of the original trabeculae by tracts of connective tissue; $\times 125$.

tissues was discovered at autopsy. Grossly, the bones appeared normal in form and structure; microscopically, generalized fibrosis was discovered, which was most marked in the tibia. Lévy did not designate by name the condition that he described, but Christeller,⁵¹ who restudied material in this case, was inclined to consider it one of acute progressive atrophy. He based his opinion on the fact that osteoblasts and osteoid tissue were practically absent in the greatly fibrosed bone. Pick described a hedgehog the skeleton of which showed nothing unusual grossly. On microscopic examination, the bones presented terrific lacunar resorption by osteoclasts, and both the compact and the spongy bone were vascularized; the enlarged canals of the blood vessels con-

49. Lévy, E.: *Arch. a. d. Geb. d. path. Anat. Inst. Tübingen* **6**:555, 1908 (pt. 2).

50. Pick, L.: *Berl. klin. Wchnschr.* **54**:797, 1917.

51. Christeller, E.: *Ergebn. d. allg. Path. u. path. Anat.* **20**:1, 1923 (pt. 2).

tained connective tissue. Fibrosis of the marrow was also present. The soft tissues showed metastatic calcification. In neither Lévy's nor Pick's animals was there any abnormality of the parathyroid glands. In rodents, progressive resorption of bones is not attended by any considerable new bone formation, so that the pathologic picture strikingly resembles that of progressive atrophy of the bone in man, no matter what the cause of the resorption.

Resorption of Bone: Its Rôle in Hyperparathyroidism.—In discussing the pathologic changes occurring in hyperparathyroidism, it was repeatedly stressed that these are brought about by progressive resorption of the original bone and replacement of it by connective tissue in which newly formed bony trabeculae appear. The newly formed trabeculae are themselves greatly subjected to resorption. Associated with the resorption is the presence of large numbers of osteoclasts in Howship's lacunae, both on the surfaces of the original bone in the process of resorption and on the surfaces of the newly formed trabeculae. Osteoclasts are present in great numbers during the active stages of the evolution of the disease. In fact, osteoclasts are more numerous in this disease than in any of the generalized malacic diseases, including even Paget's disease.

In spite of the fact that the last twenty-five years have brought to light a vast amount of new physiologic and chemical knowledge concerning many diseases—such as rickets, osteomalacia and hyperparathyroidism—some of the tenets regarding resorption laid down by histologists and cellular pathologists before these advances are still generally accepted unquestioningly as applicable without variation to every type of disease of bone. The voluminous literature on the question of bone resorption in general is so dominated by dogmatic exposition that unless one proceeds with the utmost caution in considering bone resorption in any particular disease affecting the skeleton, there are always ready pitfalls. The avoidance of these is dependent on the intelligent application of present physiologic knowledge to the interpretation of the pathologic picture.

It is plain that views concerning resorption of bone must be interpreted with due regard to the nature of the material under investigation. Thus the resorption brought about by the ingestion of acids or acid salts will differ in several ways from that due to starvation. Furthermore, Bodansky, Chandler and I⁵² demonstrated that the resorptive picture following the ingestion of an acid salt like ammonium chloride is dependent on the age of the animal, and is modified by the amount of bone-forming minerals ingested daily. In any event, the

52. Jaffe, H. L.; Bodansky, A., and Chandler, J. P.: J. Exper. Med. **56**:823, 1932.

resorptive picture in these conditions differs from that in acute inflammatory disease. The pathologic resorption of bone (that is, the resorption of bone except under physiologic conditions) has been studied for a very long time; more than one hundred years ago it was the subject of intensive investigations. These studies have brought to light that pathologic resorption proceeds with varying intensities, with even markedly different histologic pictures in different conditions. The innumerable investigations on resorption of bone have centered about the osteoclast (its origin and function), the phenomena appearing in the ground substance (including the question of preliminary decalcification) and the rôle of the vascular system (inclusive of the formation of new vessel canals in pathologic resorption—genuine Volkmann canals). More intensive consideration and evaluation of these factors will follow.

Osteoclastic Activity: Osteoclasts dominate the histologic picture in Recklinghausen's disease. Since I am opposed to the view that the osteoclast is directly responsible for the initiation of the resorption in this disease (for that matter, in any disease of bone), it is fitting here to consider the particular function of the osteoclast in the whole mechanism of the resorptive process. Pommer's views will be given in detail because of their tremendous influence on reasoning relative to resorption of bone. After von K  lliker's⁵³ recognition of the multinucleated giant cell, which he called "ostoclast" (bone breaker), in physiologic resorption, Pommer became the outstanding protagonist of its importance in pathologic processes. Beginning in 1881 he so strongly fought for the conception that the osteoclast is capable of directly eroding and removing bone without its preliminary decalcification that this view became a resorption saga in the pathology of bone. The tremendous support that accrued to Pommer's view was partly accounted for by the fact that cellular pathology was then in complete domination of conceptions in pathology. His view thereby carried tremendous influence with his contemporaries, especially with the younger pathologists being trained at that time.

In 1881, Pommer⁵⁴ declared himself to the effect that an intensive examination of his own material obliged him to support K  lliker in the view that Howship's lacunae arise through resorption by osteoclasts; he further declared that the borders of Howship's lacunae show no evidence of decalcification—thus supporting von K  lliker's view that Howship's lacunae are, without exception, delineated by normal bone

53. von K  lliker, A.: *Die normale Resorption des Knochengewebes*, Leipzig, F. C. W. Vogel, 1873.

54. Pommer, G.: *Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl.*, Wien **83-84**:17, 1881.

tissue. In 1883, he⁵⁵ again discussed this subject, stressing the view that the ground substance and bone cells are entirely passive in lacunar resorption, as in all other changes; that Howship's lacunae arise only through the activity of osteoclasts, the shapes of which conform with the adjacent Howship's lacunae, and that the osteoclasts resorb the bone by assimilating the organic ground substance and mineral salts simultaneously. In 1885, in his well known monograph on osteomalacia and rickets,⁵⁶ he pursued the same path of reasoning regarding resorption that he had previously held, only he found it necessary to expand the subject so as to discuss the rôle of the perforating canals, as well as to include—under the general theory of osteoclastic resorption—an explanation of how the osteoclasts play their part in the pathogenesis of senile atrophy, atrophy due to inactivity and the various other types of local atrophy.

He did not swerve from his original thesis: that in all types of resorption the osteoclast is the original, direct, resorbing cell; that there is never any preliminary decalcification of bone that is in the process of being resorbed, and that the bone ground substance, bone cells and processes are entirely passive. All types of atrophy he therefore conceived as arising from deficient deposition of new bone following mild degrees of osteoclastic lacunar resorption; he stated that the evidences of existing or previous lacunar resorption may be very slight and are limited to the subperiosteal region; he therefore found it necessary to reject the conception that thinning of bone in the various local atrophies results from "smooth resorption," a view that had gained considerable support and which conceived the atrophy as having arisen without osteoclastic lacunar resorption. Pommer's view of atrophy was based on the well known physiologic principle concerning growth of bone—that resorption and apposition go on throughout life—and he averred that when the deposition does not compensate for resorption, atrophy ensues.

By 1925 he arrived at the conclusion that no matter what the basis for an osteoporosis is, the process is the result of osteoclastic resorption on the foundation of a hyperemia of marrow vessels. This is greater, the more acute the process; added to this, there is the fact that new apposition does not compensate for resorption.⁵⁷ Thus, Pommer's juggling of the definition of the osteoclast, during forty years, gave to the meaning of osteoclast a variable significance. In addition to recognizing the classic type of osteoclast, he averred, particularly more

55. Pommer, G.: *Virchows Arch. f. path. Anat.* **92**:296 and 449, 1883.

56. Pommer, G.: *Untersuchungen über Osteomalacie und Rachitis*, Leipzig, F. C. W. Vogel, 1885.

57. Pommer, G.: *Arch. f. klin. Chir.* **136**:1, 1925.

recently, that small cells, with even one nucleus, seen in bone undergoing resorption may also be of the nature of osteoclasts.⁵⁸

Regarding the function of osteoclasts in resorption, it is my opinion that they must be considered aggressive, reactive, phagocytic cells which arise locally. I am not convinced that they themselves exert a dissolving influence on the bone before they remove the ground substance. On the basis of available knowledge it seems that it would be better to consider osteoclasts as bone resorbers rather than dissolvers; I should agree with Arey,⁵⁹ who takes issue with the use of "osteolytic" as a term interchangeable with "phagocytic." More accurately speaking, osteolysis by osteoclasts implies the direct dissolution of unchanged bone by these cells; phagocytosis of the bone implies the removal of changed bone. Whether osteoclasts produce osteolysis or phagocytosis of bone depends on whether the osteoclasts dissolve the inorganic salts before they remove the organic matrix. Our histologic studies of the bones of animals subjected to experimental hyperparathyroidism (especially acute) demonstrated that decalcification of bone (along the margins of the haversian canals and under the periosteum and endosteum) occurs before the decalcified matrix is removed by phagocytes. In acute hyperparathyroidism, phagocytosis may be carried on by polymorphonuclear leukocytes in addition to osteoclasts. I believe that both in chronic experimental hyperparathyroidism and in clinical hyperparathyroidism osteoclastic activity is predicated on preliminary decalcification

58. Although his views were not wholly original, they crystallized the theories of osteoclastic resorption held by many of his contemporaries. At the same time they utterly rejected a great many views held by others. A number of these had validity, but were denied acceptance by the sheer force of the repeated arguments piled up against them by Pommer. For instance, he rejected the theory of participation of the bone cells and processes, though it must be apparent to every one who has carefully studied bone in the process of resorption that the bone cells in the vicinity of the resorptive area undergo extensive changes; he held that the ground substance is entirely passive during the process of removal and shows no preresorptive changes, although any one studying ground-disk preparations of osteomyelitic or other pathologic bone will find that the enlargement of the vessel canals is accompanied by changes in the ground substance, which, in the region of the resorption, appears as large, irregular, coarse granules (Jaffe, H. L.: *Arch. Surg.* **20**:355, 1930); he consistently refused to acknowledge that preliminary decalcification of the ground substance is possible, and he held that the osteoclasts are solely responsible for removal of the calcified bone, although he never offered any evidence that this is so, except that there is a positional relationship between the osteoclasts and Howship's lacunae; he repeatedly denied the possibility in vascular resorption (when blood vessels and granulation tissue invade the haversian canals and marrow spaces) that the resorption occurs in any mode except through the endothelium of the blood vessels acting as osteoclasts. The details concerning such changes will be considered with phenomena appearing in the ground substance during resorption.

59. Arey, L. B.: *Am. J. Anat.* **26**:316, 1920.

of the ground substance. This explanation will be amplified in the succeeding pages.

Phenomena Appearing in the Ground Substance: Contrary to the point of view of Pommer and his adherents—that the ground substance, bone cells and processes are entirely passive during the resorptive process—were the beliefs of a number of other observers. Their views found the strongest protagonist in von Recklinghausen, who devoted a good portion of his important monograph on rickets and osteomalacia, published in 1910, to the exposition of the opposite point of view.⁶⁰ His treatise was the lifetime's labor of a careful investigator. His conclusions were based on the microscopic examination of undecalcified fragments of bone fixed in Kaiserling's solution or in formaldehyde solution and stained with aqueous thionine, a modification of the original method of Schmorl. There are several unfortunate features about this monograph which have led to both misinterpretation of his point of view and neglect of it. Von Recklinghausen discussed resorption of bone in general, but because he had to a great degree used rachitic and osteomalacic material the impression has been created that he conceived the true osteoid borders in these conditions to be the result of decalcification—a point which careful reading of the monograph disproves, and which was evidently far removed from his own view.

On the nature of the apparently calcium-free zones bordering calcium-bearing bone, much can be said, as observations concerning the time and the means by which calcium is deposited during the formation of bone are certainly not incontrovertible. Pommer has consistently upheld the view that every calcium-free zone (osteoid zone) bordering fully mature bone must be considered as a zone of bone which, in the process of its formation, has not as yet become calcified. In other words, it is an uncalcified zone and not one resulting from decalcification. The delimiting border between the calcium-free osteoid zone and the calcium-containing bone is a transition zone of calcified granules or a cement line (which is sharp, buckled, toothed or straight).⁶¹

Pommer's well known method for demonstrating these osteoid borders by the use of Müller's fluid for partial decalcification, followed

60. von Recklinghausen, F.: Untersuchungen über Rachitis und Osteomalacie, Jena, Gustav Fischer, 1910.

61. However, Weidenreich (*Ztschr. f. Anat. u. Entwicklungsgesch.* **69**:382, 1923) stirred up much controversy (Pommer: *Ztschr. f. Anat. u. Entwicklungsgesch.* **75**:382, 1925) when he stated that the osteoid borders may be nothing but artefacts, and that such borders are not to be found in ground-disk preparations; from this extreme view Weidenreich has apparently retreated, as in his contribution to the von Möllendorff handbook of histology he gives a more traditional discussion of these osteoid borders (von Möllendorff: *Handbuch der mikroskopisches Anatomie des Menschen*, Berlin, Julius Springer, vol. 2, pt. 2, p. 391).

by staining with basic dyes, has been applied with many other methods that demonstrate their presence. I am not fully convinced that the difference in staining between the so-called calcium-containing and calcium-free bone in osteomalacia by the Pommer method is due to the absolute lack of calcium in the latter and its presence in the former. I am inclined to believe that it may be dependent on the nature of the protein of the ground substance. By this, I do not wish to deny that quantitatively there is an absolute difference in the calcium content between them; rather, I wish to affirm that the staining differences may be influenced by other content.

Nor can I agree with Ribbert ⁶² that these differently staining zones are wholly dependent on decalcification for their origin. Using carmine, which stains the apparently calcium-free zones red, he became more or less the founder of the school that believes that there is a preliminary decalcification in all resorption of bone. However, he and those of his followers who supported him in the view that osteoid borders in all diseases of bone are the result of decalcification were undoubtedly incorrect, for in rickets and osteomalacia there is no question but that these osteoid borders are the result of deficient calcification of bone in the process of formation. Von Recklinghausen, who was in a sense a follower of Ribbert, makes plain his own distinction on this point, declaring that the designation "osteoid" should be referable only to bone that is calcium-poor or calcium-free, but at the same time he implies that such bone is in the process of progression toward calcification. Thus, he would, unlike Ribbert, exclude all borders of bone that are the result of regression or decalcification from classification as osteoid. This concurs entirely with my own view. It should therefore be apparent that no criticism of von Recklinghausen's conception of resorption of bone can be directed against him on the ground that he considered genuine osteoid borders as zones of decalcification.

However, in von Recklinghausen's description of the mechanism of resorption of bone, he introduced a large number of complicated terms which confuse and involve the explanations. Because it is important to understand clearly his use of these terms, they are summarized here. In describing the changes occurring in the bone cells and processes during resorption, he indicated that the first step in the course of their final destruction was a knobby swelling of the processes and also a swelling of the bone-cell, which he called *Onkose*. He recognized, however, that bone cells and processes may disappear without *Onkose*. In rickets *Onkose* was most considerable at the border between the original bone and the osteoid zone, while in osteomalacia it was not very abundant. About cells and processes in the *Onkose* stage he described softening of

62. Ribbert, H.: Virchows Arch. f. path. Anat. **80**:436, 1880.

the firm portion of the ground substance, and he designated the area of softening as a cell territory; he conceived this in much the same sense in which Virchow⁶³ conceived a cell territory. Territories of softened ground substance about Volkmann canals or in osteoid tissue he described as perivascular or coatlike territories.

In his consideration of the production of such territories, von Recklinghausen recognizes "thrypsis," which he defines as a slow liquefaction of the various components of the ground substance; softening sets in, which, when the cement or ground material disappears, permits such elements as the collagenous fibrils, the bone cell capsules and the sheaths of the processes to become very prominent. During this process of dissolution and softening, the various components of the ground material appear as fragments or granules; afterward, there is complete disappearance of the ground substance, owing to shrinkage and liquefaction. Von Recklinghausen made this distinction between thrypsis and halisteresis: Thrypsis defines the inclusive process of dissolution of the ground substance of bone (whether or not the bone is calcified), while halisteresis is a part of the all-inclusive process of thrypsis which specifically relates to the solution of the calcific or mineral elements of the ground substance.

One of the points in the von Recklinghausen concept on which there has been much controversy is the interpretation of the *Gitterfiguren* (lattice-figures), which, according to him, are the consequences of softening of bone tissue, whether osteoid or completely calcified. He conceived these figures to be the result of thrypsis. He demonstrated their presence by filling with gas the lattice spaces that result in ground substance undergoing thryptic liquefaction. Thus, *Onkose*, cell territories and the lattice-figures were regarded as evidence that thrypsis was taking place.

He held that if microscopic evidences of thrypsis are observed in bone that contains calcium, it is necessary to conceive that at the onset of the thryptic disintegration the mineral portions had to be dissolved out. This he considered as an indirect proof of the occurrence of halisteresis. Finally, von Recklinghausen stated that he could not give positive information concerning the celerity with which disintegration of the ground substance occurred. In considering the entire process of thrypsis in rickets and osteomalacia, he tried to show that whenever it was present the bone involved had to be considered as bone in the course of destruction. Such appearances could be seen on the surfaces of mature bone undergoing decalcification. Furthermore, thrypsis could also be observed in genuine osteoid tissue. When genuine osteoid tissue shows evidences of thrypsis, it is undergoing dissolution. Von Recklinghausen

63. Virchow, R.: *Die Cellularpathologie*, Berlin, A. Hirschwald, 1871, vol. 1.

also indicated that very slight signs of thrypsis may, on careful examination, be observed in normal bone during the process of growth. In regard to rickets and osteomalacia, he made the significant comment that much of the genuine osteoid tissue that is formed in these diseases never goes on to calcification, even though the lesion may heal; much of this osteoid tissue has to be removed. He had observed, as many others had, that osteoclasts do not play a significant rôle in the resorption of rickets and osteomalacia.

This brings one directly to the problem of the occurrence of thrypsis and halisteresis in hyperparathyroidism. In our ⁶¹ experimental studies of hyperparathyroidism, the mechanism by which the original and newly formed bone is removed had always been of particular interest to us. It is well known that parathyroid extract-Collip produces a disturbance in the acid-base equilibrium, and its injection leads to an increased excretion of the mineral salts, especially calcium and phosphorus, particularly through the urine. This histologic study of a great number of fixed and decalcified bone sections (as well as ground-disk preparations) from animals suffering from experimental hyperparathyroidism has led us ⁶⁴ to the conclusion that hyperparathyroidism (as a result of the changes that it induces in the tissue fluids circulating about the bone) has but one primary effect on the bone: the solution of mineral salts out of the bone, at the surfaces of contact between the tissue fluid and the bone. The immediate effect of hyperparathyroidism is the disappearance of osteoblasts from the surfaces of the normal bone, where bone formation is normally in progress. This is most apparent where new bone formation is most active. From our observations we have been led to conclude that all other appearances and effects are secondary to the cessation of new bone formation and the associated production of minute and narrow zones of decalcification on the subperiosteal, sub-endosteal, trabecular and haversian canal surface. Even in an animal like the rat, in which osteosclerosis may eventually develop, resorption continues throughout the course of treatment with parathyroid.

We have been able to convince ourselves that thrypsis and halisteresis are at the basis of this primary decalcification, as in favorable specimens (especially when severe, acute hyperparathyroidism had existed) swelling of the bone cell lacunae and disintegration of their nuclei were observed in narrow decalcified zones; this occurred even in the absence of osteoclasts. Furthermore, ground-disk preparations invariably showed that the ground substance in these narrow zones contained large granules. Occasionally, we have observed, especially in acute hyperparathyroidism, that polymorphonuclear leukocytes had begun actively to phagocytose the decalcified organic matrix, sometimes

64. Jaffe and Bodansky.^{30a} Jaffe, Bodansky and Blair.^{30c} Jaffe, Bodansky and Blair.^{30e} Jaffe, Bodansky and Blair.⁴²

even in the absence of osteoclasts. Osteoclasts could be seen forming from the marrow connective tissue adjacent to the decalcified bone margins, and these osteoclasts rapidly proceeded to phagocytose the decalcified organic matrix, with the production of deep lacunae of Howship.

As the chronic hyperparathyroidism proceeded, especially in as susceptible an animal as the dog, the number of osteoclasts became quite numerous. Both in clinical and in experimental hyperparathyroidism, great numbers of osteoclasts appear, because both the original bone and any newly formed bone that may appear in the connective tissue are constantly subject to drastic decalcification, and the osteoclasts arise to carry on the phagocytosis of the decalcified matrix.

Abnormal Vascularization: Changes in the Canals of Blood Vessels: In Recklinghausen's disease, the resorption of the bone is accompanied by enlargement of the existing canals of blood vessels. Abnormal numbers of perforating canals, in the sense in which Volkmann⁶⁵ described them in inflammatory diseases, do not appear. Regarding the perforating canals, Pommer also correlated their origin with the theory of osteoclastic resorption, stating that such canals are channels prepared for blood vessels and that they arise in mature bone tissue through the resorbing activity of the vessel sprouts. In their incipient stages, these sprouts are conceived by him as solid protoplasmic masses that function as osteoclasts in the process of resorption. They produce a passage for a blood vessel; finally the vessel arises through a space developing in the protoplasmic mass. The protoplasmic mass may be aided in the resorption of the formed bone by osteoclasts. Pommer made a distinction between true and false perforating canals, based on histologic appearances; he held that a true perforating canal has a pointed protoplasmic mass at its head, and that it is not surrounded by any accompanying lamellae; he further stated that only the true perforating canals could be considered as resorption canals, newly formed in mature bone.

The large and exhaustive literature that exists concerning the nature, the mode of origin and the histologic appearances of these canals is sufficient to tax the patience of any investigator, let alone the vast amount of print that is devoted solely to polemics. The controversy that has more recently developed between Zawisch-Ossenitz⁶⁶ (who was supported by her teacher, Schaffer) and Pommer⁶⁷ concerning the perforating canals has again opened the subject. On the basis of her studies, Zawisch-Ossenitz concluded that all anastomosing canals within

65. Volkmann, R.: *Arch. f. klin. Chir.* **4**:436, 1863.

66. Zawisch-Ossenitz, C.: *Ztschr. f. mikr.-anat. Forsch.* **6**:76, 1926; **9**:585 and 606, 1927.

67. Pommer, G.: *Ztschr. f. mikr.-anat. Forsch.* **9**:540, 1927.

bone that have no smooth borders are perforating canals and that there is no need of distinguishing, as Pommer did, between true and false perforating canals. Furthermore, she observed that in the formation of perforating canals the bone ground substance a little in advance of the blood vessel or cellular sprout was in a stage which she called "preresorptive"; finally, she stated that the vessel in a perforating canal may degenerate and the canal then be filled with young bone or, more rarely, left empty.

In Pommer's polemic reply,⁶⁸ he reaffirmed his views concerning the perforating canals, and stated that the material which Zawisch-Ossenitz used in her investigations was not that best suited for such investigation, as it was mostly embryonal bone. For this criticism of her work there is some basis, as perforating canals in the sense that Volkmann described them are newly formed canals appearing in pathologic adult bone. In a discussion of the canals of blood vessels in normal and pathologic bone, I⁶⁹ attempted to clarify the distressingly confused issues concerning the nature and the mode of origin of pathologic canals. Nevertheless, such changes in the canals, although important in certain resorptive phenomena, are of minor significance in the resorptive picture of Recklinghausen's disease.

Pathogenesis of the Resorption of Bone in Hyperparathyroidism.—Herein it is my endeavor to explain the phenomena operating to produce the resorptive picture. As far as the bones are concerned, their resorption (decalcification, removal and thinning) depends on the extraction of minerals from their substance, causing a concomitant diminution in the actual bone substance. It seems probable to me that when the state of hyperparathyroidism is initiated, the minerals are first withdrawn from the soft tissues and excreted; this demands mobilization and withdrawal of the minerals from the bones, which partly compensates for the extraction of the minerals from the soft tissues. Hyperparathyroidism induces a state of acidosis, which requires compensation through the withdrawal of large stores of earthy alkaline substances from the bones. The manner in which the mineral stores are mobilized from the bones remains uncertain; there is, however, reason to believe that in hyperparathyroidism the tissue fluids circulating about the bone are so modified as to favor removal of minerals from the bone rather than their deposition. Following this decalcification, or halisteresis, osteoclasts proliferate to phagocytose the decalcified bone matrix, and marrow fibrosis ensues as part of the reaction to the changed status of the bone structure. It is evident that the continuation of such a state (chronic hyperparathyroidism, either clinical or experimental) leads to further

68. Pommer, G.: Ztschr. f. mikr.-anat. Forsch. **11**:283, 1927.

69. Jaffe, H. L.: Am. J. Path. **5**:323, 1929.

halisteresis, or decalcification, more pronounced resorption through osteoclastic proliferation and additional marrow fibrosis—all of which produce the advanced pathologic picture seen in Recklinghausen's disease.

Albright and Ellsworth⁷⁰ offered an explanation of skeletal decalcification which strikes me as failing to account for the initial source of change. Investigation of patients with clinical Recklinghausen's disease and patients with hyperparathyroidism induced by the injection of parathyroid extract-Collip led them to conclude that the basis for the pathogenesis of the decalcification is a disturbance of phosphorus metabolism. They coordinated the frequently depressed serum phosphorus level and the raised serum calcium level (in patients with clinical hyperparathyroidism) with a primary lowered renal threshold for excretion of phosphorus. In a number of papers⁷¹ it was suggested that in both clinical and experimental hyperparathyroidism the increased excretion of calcium may be dependent on an increased excretion of phosphorus, leading to depletion of the phosphorus in the body fluids. As stated, they attributed the whole cycle of change primarily to a lowered renal threshold for phosphorus, induced by the hyperparathyroidism. However, the question is not so simple as these investigators would lead one to believe.

Their hypothesis presumes that the abnormality in the relation of the calcium ion to the phosphate ion in the serum in hyperparathyroidism is dependent on changes in the excretion of phosphorus through the urine. To them the state of hyperparathyroidism is first manifested by an increased urinary excretion of phosphorus. According to these workers, this is the beginning of a cycle which is marked by a decreased amount of inorganic phosphorus in the serum; this creates a tendency for subsaturation of the serum with calcium phosphate; this, in turn, leads to the mobilization of calcium phosphate from the bones to compensate; finally, the serum calcium level is raised, the urinary excretion of calcium is increased and the serum phosphorus level continues depressed because of the existence of the lowered renal threshold for phosphorus. These conclusions were based on metabolic studies of patients given injections of parathyroid extract-Collip. Their formula concerning the pathogenesis of the bone changes of clinical Recklinghausen's disease is based on these assumptions. They do not, however, give consideration to any of the numerous histologic phenomena that occur in the bones, nor do they explain how this apparent change in the renal threshold for phosphorus brings about the bone changes observed in hyperparathyroidism.

70. Albright, F., and Ellsworth, R.: *J. Clin. Investigation* **7**:183, 1929.

71. Albright, Bauer, Ropes and Aub.²⁶ Albright and Ellsworth.⁷⁰ Ellsworth, R.: *J. Clin. Investigation* **11**:1011, 1932.

Furthermore, it is impossible to suppose that the rise in serum calcium after the injection of parathyroid extract-Collip is necessarily dependent on a decrease in serum phosphate—which inverse relationship is frequently accepted as the usual response following the injection of parathyroid extract-Collip in the normal dog or man. Thomson and Pugsley⁷² more recently showed that in normal dogs the total serum inorganic phosphate may either increase slightly or remain constant after the injection of parathyroid extract-Collip. From their experiments they conclude that in the dog the rise in serum calcium after the injection of parathyroid extract is not secondary to a fall in the serum phosphate. If the renal threshold for the excretion of phosphate is affected, they believe that the change is not reflected in the composition of the blood. Bodansky and I^{31b} demonstrated that the injection of a single moderate dose of parathyroid extract-Collip into puppies suffering from chronic hyperparathyroidism raised the serum phosphorus (within nine hours and earlier). Sometimes the increase of serum phosphorus was the earliest response in the blood and frequently the only response to a single injection of parathyroid extract-Collip in such dogs, while the serum calcium rose slightly, if at all. Thus, the assumption by Albright and Ellsworth that the lowered renal threshold leads to diminished serum phosphorus and increased serum calcium does not always hold.

Another theory has also been proposed: that hyperparathyroidism leads to decalcification of bone because the parathyroid secretion itself makes the plasma a better solvent for the bone minerals. Greenwald and Gross²⁷ suggested that an organic substance secreted by the parathyroid gland, identical with the parathyroid hormone formed under its influence, circulates in the plasma and unites with calcium ions to form an undissociated compound. According to them, the administration of parathyroid extract-Collip directly or indirectly increases this organic substance, thus reducing the concentration of calcium ions in the plasma and permitting the liberation of more calcium ions from the bone. This point of view would imply that the plasma behaves as if in equilibrium with the solid calcium-phosphorus compounds in the bone. It would be difficult to explain, on the basis of this view, how it is possible to attain a hypocalcemia with increased injections of parathyroid extract-Collip such as Bodansky and I^{31b} observed in a dog on a low intake of calcium. Furthermore, the hypocalcemia was associated with a progression of the decalcification.

My colleagues and I therefore wish to reaffirm our own view, which attributes the entire sequence of changes that lead to the resorption of bone in hyperparathyroidism to a decalcification (halisteresis) caused by modified tissue fluids circulating about the bone. Only after this do other changes proceed in the bone. Extensive new bone formation occurs,

72. Thomson, D. L., and Pugsley, L. I.: *Am. J. Physiol.* **102**:350, 1932.

especially in rats, even while the resorption continues. On the other hand, Thomson and Collip⁷³ and Thomson and Pugsley⁷² have held that the most acceptable theory of the action of parathyroid extract-Collip is that it directly stimulates the osteoclastic process. The osteoclasts, accordingly, erode the bone and liberate the mineral salts. They came to this conclusion because in experimental hyperparathyroidism numerous osteoclasts are to be observed in bone sections. Nevertheless, had they carefully studied large series of bone sections, they would frequently have found evidences of decalcification (haliteresis) before osteoclasts appeared. We agree with these authors that the changes in the bone in hyperparathyroidism are the result of local effects. However, we have found that osteoclasts arise to phagocytose the bone matrix only after it has been decalcified. We have also found that osteoclasts appear in as great numbers as they do in hyperparathyroidism under circumstances that cannot in any way be related to stimulation by parathyroid extract. Bodansky, Chandler and I⁵² produced a histologic picture in many ways simulating that observed in chronic experimental hyperparathyroidism when we fed young, growing dogs a diet low in calcium (with or without the additional administration of ammonium chloride). Besides, in unpublished experiments, we also found that diets high in phosphorus which produced a marked disturbance in the calcium-phosphorus intake ratio also led to the appearance of numerous osteoclasts. This again could not be attributed to stimulation by parathyroid extract-Collip.

Relation of Certain Experimental Dystrophies to Those of Hyperparathyroidism.—Long before Recklinghausen's disease was recognized, experiments were undertaken on the dystrophic effects on the skeleton of calcium starvation. These experiments were instituted principally to ascertain the relation between experimental calcium deficiency and clinical rickets. Many of the early investigators who applied themselves to an experimental study of calcium deficiency believed that rickets had developed in their animals. Voit⁷⁴ fed puppies on fresh meat or meat extract, lard and distilled water. Deformities of the bones, especially of the legs, set in; there was curvature of the spine; the chest was flattened; the pelvis was narrowed and sunken; the animals were very weak, and after a hundred and fifty-three days they could not walk. At autopsy, there were multiple fractures and swelling at the costochondral junctions. On macroscopic grounds Voit considered the lesions as rachitic. The controls, receiving bone ash in addition, showed none of these lesions. It remained for Korsakoff⁷⁵ to point out that, although the macroscopic lesion produced in puppies on such a diet resembled

73. Thomson, D. L., and Collip, J. B.: *Physiol. Rev.* **12**:309, 1932.

74. Voit, E.: *Ztschr. f. Biol.* **16**:55, 1880.

75. Korsakoff: *Zur Frage von der Pathogenese der englischen Krankheit*, Dissert., Moscow, 1883.

rickets, microscopically the lesion was not rickets, as the osteoid zones on the trabeculae were thin, and the epiphyseal cartilage plates were not markedly thickened. Miva and Stoeltzner ⁷⁶ concluded that such lesions were of the nature of pseudorachitic osteoporosis, with fibrosis of the marrow. In the course of our studies, Bodansky and I ^{50a} fed young, growing puppies a calcium-deficient diet consisting of lean meat to which were added adequate quantities of tomato juice and cod liver oil (to protect the animals from rickets and scurvy). The animals grew well, but developed thin bones which fractured easily. After several months on this regimen, histologic examination of the bones showed extensive osteoporosis, considerable marrow fibrosis, some new bone formation in the marrow connective tissue, numerous osteoclasts in Howship's lacunae on the original and on the newly formed bones and slight widening of the proliferating cartilage zones. On the whole, the histologic appearance was different from what may be expected in rickets. The lesion, depending on its severity, ranged from a marked osteoporosis to a condition that could be distinctly called generalized osteitis fibrosa.

It is obvious that the gross and microscopic pathologic pictures as observed by the different investigators who studied the effects of calcium deficiency on the growing animal should have varied. Most earlier workers gave no consideration to the question of vitamin content. Some of the early investigators noted that the lesion appearing with a diet of lean meat plus carbohydrates were more severe than when the meat diet was supplemented with lard. Furthermore, variation in the fat content of the meat itself may account for some of the differences in the bone lesions, as muscle fat has a slight antirachitic potency. In harmony with this are the observations of Weber and Becks,⁷⁷ who fed growing puppies a synthetic diet, poor in calcium and free from vitamin D; they observed all the fibrous bone lesions described, plus giant cell tumors and pseudocysts about the roots of the teeth. This brings out the fact that the more drastic the diet, the more pronounced are the bone changes. In young dogs receiving an inadequate amount of calcium plus ammonium chloride (but protected against rickets and scurvy), Bodansky, Chandler and I ⁵² produced severe decalcification and resorption of bone and such marked marrow fibrosis that the resultant histologic picture could be designated as generalized osteitis fibrosa.

Thus, when there is a drastic deficiency of calcium due to an inadequate intake, the changes in the bones may, with some minor variations, approach those produced by chronic hyperparathyroidism. Hyperparathyroidism affects bones by abstracting their minerals. The ultimate effect of both treatments on the bones may show considerable similarity.

76. Miva, S., and Stoeltzner, W.: Beitr. z. path. Anat. u. z. allg. Path. **24**:578, 1898.

77. Weber, M., and Becks, H.: Virchows Arch. f. path. Anat. **283**:752, 1932.

By this I do not mean to suggest that the two conditions are analogous. Hyperparathyroidism, while it abstracts the minerals from the bones, produces a hypercalcemia and often toxic changes in other tissues with metastatic calcification. On the other hand, the severe decalcification, resorption and fibrosis of the bones that result from a diminished intake of calcium are associated with a tendency for the level of the serum calcium to be below normal (sometimes tetany appears, owing to the hypocalcemia). The changes in the bones in both of these conditions are nothing more than an index of the calcium deficiency, produced, however, by two entirely different etiologic factors. While the bone lesions resulting from the administration of parathyroid extract-Collip are, in a broad sense, of the same histologic appearance as those produced in young, actively growing dogs on a diet low in calcium (but otherwise adequate), other important differences are noted. For instance, the dogs that are given parathyroid extract-Collip show stunting of growth, while those on a diet the calcium content of which is inadequate grow satisfactorily if the deficiency of calcium is not too drastic.

Relation of Generalized Osteoporosis to Generalized Osteitis Fibrosa.—One must conceive of generalized osteitis fibrosa as a rather inclusive category. Not only does it embrace the advanced clinical form of Recklinghausen's disease (which has a specific parathyroid etiology) and the experimentally produced osteitis fibrosa of similar origin; but it likewise covers the experimentally produced forms of generalized osteitis fibrosa which are caused by other means, and in which there is rapid resorption with resulting marked connective tissue proliferation in the marrow. Furthermore, in normal puppies, the amounts of calcium adequate for slow growth may, if these puppies are growing actively, produce a histologic picture of osteitis fibrosa different only in quantitative aspects from that which appears in rapidly growing puppies on a diet containing an inadequate amount of calcium. Thus, either clinically or experimentally, if decalcification of bone is rapid, no matter what the etiology—and this would apply either to the young or to the adult—generalized osteitis fibrosa occurs. From this point on there may be modification of both the gross and the histologic features of the osteitis fibrosa, owing to the special underlying factor inducing the decalcification. This makes it conceivable that hyperparathyroidism may, in the course of the development of osteitis fibrosa, incidentally favor extensive hemorrhage into the marrow, resulting in brown blood cysts and the formation of giant cell tumors. It is known that generalized osteitis fibrosa (Recklinghausen's disease) may exist without cysts and giant cell tumors.

On the other hand, a slowly developing decalcification, from whatever cause, will lead, in both the young and the adult patient, to a less severe resorption; this lesion is called osteoporosis, because of the

absence of striking fibrosis. The occurrence of osteoporosis in adults under a number of circumstances is well known, and one of the most common causes, aside from senility, is exophthalmic goiter. In this disease there is a negative mineral balance, but the patients usually do not suffer from the effects of a diminished intake of calcium. The disease is chronic and the resorption is slow but progressive.

The modifying effects of several factors on the bone lesion are further illustrated in experimental rickets. It is well known that rickets cannot be produced experimentally in rats by withholding vitamin D unless there is simultaneously a dietary mineral imbalance (disturbance of the calcium-phosphorus ratio). In very young, rapidly growing rats given a curative vitamin D supplement but a diet low in calcium a generalized osteitis fibrosis will develop. On the same regimen with much more vitamin D (short of toxic dosage) the marrow fibrosis will be essentially prevented, and simple generalized osteoporosis will ensue. The same diet with the exclusion of vitamin D will produce rickets. In addition, the greater the disturbance of the calcium-phosphorus ratio in the diet, the larger are the requirements for vitamin D.⁷⁸ These commentaries explain the development of the pathologic picture of osteoporosis rather than osteitis fibrosa or vice versa; the difference depends chiefly on the celerity with which the resorption occurs.

While the experiments noted have yielded comparisons mostly on regimens low in calcium and high in phosphorus, it is recognized that similar results can be obtained with a different type of calcium-phosphorus imbalance, namely, a diet of low phosphorus and high calcium content. It is well known that in certain regions where the grass has a low phosphorus content, osteophagia develops in cattle, with extreme skeletal decalcification and increased serum calcium and low serum phosphorus values.⁷⁹

The changes in the bones of animals with spontaneous osteitis fibrosa resemble in many ways, but frequently do not duplicate, those observed in the fibrous osteodystrophies of man. Peculiar to some animals with fibrosed bones is the common appearance of obstruction of the nasal and oral cavities; these are encroached on by thickening of their walls. As a result, such animals may have sniffling respiration. However, fibrous lesions of the bones exist in animals not afflicted with sniffling respiration. Christeller,⁸¹ Rehn,⁸⁰ Hintze,⁸¹ Busolt⁸² and Ingier⁸³

78. Bethke, R. M.; Kick, C. H., and Wilder, W.: *J. Biol. Chem.* **98**:389, 1932.

79. Palmer, L. S., and Eckles, C. H.: *Proc. Soc. Exper. Biol. & Med.* **24**:307, 1927. Robertson, W.: *J. Comp. Path. & Therap.* **18**:114, 1905.

80. Rehn, E.: *Beitr. z. path. Anat. u. z. allg. Path.* **44**:274, 1908.

81. Hintze, R.: *Arch. f. wissenschaft. u. prakt. Tierh.* **35**:535, 1908-1909.

82. Busolt: *Schnueffelkrankheit der Schweine*, Dissert., Giessen, 1913.

83. Ingier, A.: *Frankfurt. Ztschr. f. Path.* **12**:270, 1913.

described swine, goats, cattle and horses which showed either true generalized osteitis fibrosa or a local form of osteitis fibrosa. In most instances only the skull was studied, but in a limited number a complete examination of the skeleton was made, and generalized osteitis fibrosa was found. Koch⁸⁴ and Christeller observed spontaneous osteitis fibrosa in monkeys, Koch pointing out that the condition had been previously confused with rickets.

Dogs are also subject to spontaneous osteitis fibrosa. Christeller described a dog the bones of which were thin and porotic, the long tubular bones showing curvature and diminished longitudinal growth. The lesions were most prominent in the upper and lower portions of the diaphyses, where there was fibrous replacement of the marrow, transformation of the existing bone, new bone formation and resorption of bone with numerous Howship's lacunae and osteoclasts. The haversian canals of the cortex were widened and invaded by fibrous tissue. The epiphyseal cartilage plates were present, and relatively normal endochondral ossification was still in progress. The entire skeleton was involved, but the ribs relatively showed the greatest alterations. Schmey⁸⁵ and Pick⁸⁶ described an atrophic deforming generalized disease of bone in senile dogs with a predominance of osteoporosis but with little fibrosis. Hager⁸⁷ described an instance of osteitis fibrosa in a dog in which the upper and lower jaws were tremendously enlarged. Weber's⁸⁸ dog, 8½ months of age, had spontaneous fibrous osteodystrophy with thickened porotic bones, cysts and giant cell tumor formations. The jaw of the dog was also enlarged and cystic. The parathyroids were normal, and calcium metastases were not observed.

It is difficult to attribute any specific connotations to this miscellaneous collection of spontaneous fibrotic diseases in animals. Often the examination was made by one who saw the bones only after the animal's death; frequently no history was available. It is fair to surmise that some fundamental disturbance in metabolism was at the root of the changes described. If not a disturbance in mineral intake, it may have been a condition related to a disturbance of the gastrointestinal tract (such as diarrhea, which in effect could produce the same changes). The sniffling respiration is a complication that is to be attributed to local infection in an animal suffering from the bone lesions indicated.

84. Koch, J.: *Verhandl. d. deutsch. path. Gesellsch.* **13**:107, 1909.

85. Schmey, M.: *Virchows Arch. f. path. Anat.* **220**:52, 1915.

86. Pick, L.: *Berl. klin. Wchnschr.* **68**:797, 1911.

87. Hager, O.: *Ueber einen Fall von Ostitis fibrosa beim Hunde*, Dissert., Giessen, 1919.

88. Weber, M.: *Beitr. z. path. Anat. u. z. allg. Path.* **82**:1, 1929.

The Parathyroid in Recklinghausen's Disease.—In the introduction of this paper, the evolution of knowledge concerning the relation of parathyroid enlargement to diseases of bone was traced. Emphasis was laid on the various advances leading up to the present understanding of the subject, and an evaluation was made of the significance of these contributions. From all these emerged one fact of dominating importance: *Parathyroid enlargement with parathyroid hyperactivity was proved to be the primary basis (both etiologically and pathogenically) for generalized osteitis fibrosa cystica, or Recklinghausen's disease.*⁸⁹

Accumulated postmortem and clinical experience with this disease demonstrated the variability of the number, size, position and gross and histologic appearance of such enlarged parathyroid glands. Postmortem experience has also shown that in some cases one enlarged parathyroid gland was the only parathyroid tissue found, even in careful dissection; in other cases one or more (in some instances even four) normal parathyroid glands were found, even in the presence of an offending enlarged parathyroid. When normal parathyroid glands were not

89. It is rather amazing that in spite of the accumulated evidence, on pathologic, clinical and experimental grounds, that Recklinghausen's disease is distinct and separate from other malacic diseases (as for instance, osteomalacia and osteoporosis), there are many who as yet do not accept it as an entity. Looser, even as late as 1928, stated that cysts and giant cell tumors of bone (whether solitary or multiple) are local posttraumatic formations, which occur both in normal and in extensively diseased bone (Looser, E., in Schinz: *Lehrbuch der Röntgen-Diagnostik mit besonderer Berücksichtigung der Chirurgie*, Leipzig, Georg Thieme, 1928, p. 243). He could not accept their presence in a malacic condition of bone as indicating a special disease. To him, fibrous osteitis was only a symptomatic process that might be produced by many conditions; therefore, since cysts and giant cell tumors, if present, were not significant as indicating a particular feature of the malacic disease, Recklinghausen's disease per se could not exist. Looser's conclusions concerning the mode of origin of cysts and giant cell tumors were based on roentgenologic examinations; similarly his conclusions concerning Recklinghausen's disease were not based on pathologic studies. By 1932, he was impelled to modify this stand, accepting Recklinghausen's disease as an entity. Lang and Häupl (*Virchows Arch. f. path. Anat.* **262**:383, 1926) stated that the pathologic changes of Recklinghausen's disease are simply the result of pathologic irritation of poorly calcified bone, and that similar changes may be observed in the bone and bone marrow in osteoporosis, osteomalacia and rickets. Lang (*Beitr. z. path. Anat. u. z. allg. Path.* **87**:142, 1931), reaffirming this stand, added that the osteitis fibrosa of Recklinghausen's disease is nothing else than the consequence of bone and marrow fibrosis subsequent to pronounced osteoporosis. In regard to the view of Lang and his co-worker, there can be no doubt that the fibrous tissue reaction in rickets and osteomalacia is the consequence of mechanical and static deficiencies in weakened bone. To stretch the explanation of the nature of the connective tissue response in these diseases to cover the connective tissue response in Recklinghausen's disease as being of no other significance seems far fetched in view of the established parathyroid pathogenesis for the latter condition.

found, it is conceivable that they had undergone involutional atrophy because of the presence of an enlarged hypersecreting gland. It is equally possible that the enlarged parathyroid was the only one formed embryologically. In any event, these pathologic findings indicate the danger of parathyroid tetany following operative removal of an enlarged gland. One of the striking features so far brought out in the studies of the relation of parathyroid tumors to Recklinghausen's disease is that they are benign. There is danger of interpreting a benign tumor as malignant, as Wellbrock⁹⁰ did, because of certain atypical histologic appearances.

The variability in the size and weight of the parathyroid tumor (or tumors) has been considerable; they have measured from 1 to 7 cm. in the greatest diameter; each of the two adenomas in Paul's case weighed as much as 35 Gm.⁹¹ No correlation has been established between the size of the offending parathyroid tumor and the severity of the disease. In spite of their large size, it is amazing that so few of them could be palpated before operative removal; some of the largest glands were not palpable because they were tucked away behind the thyroid (between the esophagus and trachea).

The parathyroid tumors are often diversely situated, sometimes far removed from the expected position; this is quite in accord with the fact that even the normal parathyroid glands may vary extremely in their anatomic locations. Hypersecreting parathyroid adenomas have even been found completely within the substance of the thyroid gland, as well as in the mediastinum.

The enlarged parathyroid gland is usually nodular and cystic; microscopic cysts predominate (such cysts may even be observed in normal parathyroid glands), but frequently the cysts are large enough to be recognized grossly; the cut surface appears yellowish. The microscopic appearance of such an enlarged parathyroid may in places be so changed as to lose all semblance of normal parathyroid tissue. In such areas, the cells and also the nuclei are usually very much enlarged; giant or multiple nuclei may be observed within some of the enlarged cells. In such abnormal areas, the protoplasm of the cells may show varying degrees of density. Even within these areas, nests of water-clear principal cells may be seen. Among the other appearances that may sometimes be observed are alveolar formations with colloid-like contents, foci of small cells with pyknotic nuclei and any number of other abnormalities induced by degeneration within the enlarged gland. In the nondegenerated areas of the parathyroid tumor, the principal cell usually predominates. However, some of the para-

90. Wellbrock, W. L. A.: *Endocrinology* **13**:285, 1929.

91. Paul, F.: *Beitr. z. path. Anat. u. z. allg. Path.* **87**:503, 1931.

thyroid tumors have been described as composed, for the most part, of oxyphil cells; it seems nevertheless beyond doubt that the oxyphil cells are derived from the principal cells, and that pale oxyphil cells can lose their histologic peculiarities and become indistinguishable from the ballooned-out principal cells. Even when either the principal or the oxyphil cells predominate, some of the other cells are usually to be seen. Most of the tumor cells are free from fat, but if fat is present in them it exists in the form of fine granules.

Discussion as to whether the parathyroid tumor is the result of a compensatory hyperplasia or whether it is an adenomatous new growth seems to me to have been entirely settled in favor of the latter. This view is supported by the fact that removal of such tumors in Recklinghausen's disease leads to prompt clinical improvement, with correction of the bone lesions, when all the offending tissue is extirpated. For the sake of discussion, one may, of course, grant that in glandular organs compensatory hyperplasia may be histologically indistinguishable from adenomatous new growths. The usual gross anatomic distinction that is made in regard to an adenoma (that it is an encapsulated spherical mass situated within the tissue in which it arises) does not necessarily apply to the parathyroid gland. It must be plainly evident that an adenoma arising in a parathyroid gland may grow to such proportions as completely to destroy and replace the tissue in which it originated.

Compensatory Parathyroid Enlargement: In Recklinghausen's disease, the enlarged parathyroid is a tumorous new growth; but parathyroid enlargement may occur under a number of circumstances on the basis of a compensatory reaction. This is occasionally observed in genuine osteomalacia. A similar explanation seems to hold for the parathyroid enlargements that may at times occur in certain cases of senile osteoporosis, hunger osteopathy, multiple myeloma, clinical and experimental rickets and chronic nephritis, and in the presence of multiple carcinomatous skeletal metastases. In such cases, the enlargement generally involves all four, or the two main glands, but may be limited to only one. The last form is the least common. MacCallum¹⁷ observed a cystic parathyroid mass, 2 cm. in diameter, in a young man who suffered from chronic nephritis for years. The enlarged parathyroid was opaque and whitish yellow, and on microscopic section differed in no way from normal parathyroid tissue, except that no fat cells were present between the cell strands. The pathogenesis for such enlargement cannot be definitely assigned; it may possibly be the index of an effort to secrete more of the active parathyroid principle (which, within certain physiologic limits, undoubtedly exercises a beneficial effect on calcium metabolism and aids in the absorption of minerals from the intestinal tract). The secretion at the same time probably assists in a better economy of these minerals after absorption;

possibly it helps in the maintenance of normal serum calcium values when abnormal drainage of the mineral stores takes place.

Malignant Parathyroid Growths: It is difficult to decide whether malignant tumors of the parathyroid occur. The tumors described by Benjamins⁹² and Hulst⁹³ were located within the thyroid gland; they had been removed surgically; no mention was made of the condition of the bones. Such tumors exhibit local malignant characteristics and may metastasize. Langhans⁹⁴ designated them as "parastruma"; they are probably carcinomas of the thyroid; within their substance they may show thyroid tissue; histologically their cells resemble the principal cells of the parathyroid. It therefore remains doubtful whether malignant tumors of the parathyroid gland have thus far been reported.

Other Tissue Changes in Recklinghausen's Disease.—Metastatic calcification is the significant pathologic alteration that has been noted in the soft tissues in some cases of hyperparathyroidism. In Dawson and Struthers'²⁰ case, calcium deposits, in the form of fine granules, which in some instances became confluent masses, were present in all the internal organs and in all tissues of the body. The arteries in their case were also calcified. This was an unusually pronounced example of metastatic calcification; more frequently, if present at all, it is limited to the lungs, gastric mucosa and kidneys. Since metastatic calcification was first recognized, these sites have been known to be favored for the depositions. Their predisposition to the precipitation of salts of calcium is attributed to the existence of an intense local alkalinity in these tissues as they are sites of considerable acid excretion. In the lungs, the calcific deposits are observed mainly in the connective and elastic tissue of the alveolar walls, in the capillary walls and sometimes in the elastic fibers of the small arteries and veins; in the gastric mucosa, the interglandular tissue is chiefly infiltrated, especially in the acid-secreting portion; in the kidneys, calcium is deposited especially in the tubular epithelium, although the connective stroma may demonstrate calcific incrustations.

Since Virchow's⁹⁵ original description of metastatic calcification, it has been held that renal disease seems to be a necessary concomitant for the production of the calcium deposits. Barr⁹⁶ recently reviewed this subject, collecting forty-two instances of miscellaneous spontaneous metastatic calcification. In this varied group, he noted that the absence of renal involvement was exceptional. Dawson and Struthers' patient, with metastatic calcification of most intense degree, did not have nephri-

92. Benjamins, C. E.: Beitr. z. path. Anat. u. z. allg. Path. **31**:143, 1902.

93. Hulst, J. P. L.: Centralbl. f. allg. Path. **16**:103, 1905.

94. Langhans, T.: Virchows Arch. f. path. Anat. **189**:69, 1907.

95. Virchow, R.: Virchows Arch. f. path. Anat. **8**:103, 1855.

96. Barr, D. P.: Physiol. Rev. **12**:593, 1932.

tis. The deposition of calcium in the lungs of the new-born (on a congenital basis) has occasionally been reported.⁹⁷ There is still uncertainty as to whether local tissue damage precedes the calcific depositions. Those who favor its occurrence believe that the overloading of the tissue fluids with calcium is insufficient in itself to determine the deposition of the mineral, even in sites of intense local alkalinity. At the present time, no all-embracing explanation of the phenomena underlying metastatic calcification can be offered.

While metastatic calcification is extremely rare as a postmortem finding, it was recently discovered that it could easily be produced with toxic doses of parathyroid extract-Collip or viosterol. In the dog, overdosage of parathyroid extract produces vomiting, diarrhea, hematuria, hemorrhagic gastro-enteritis, renal impairment and metastatic calcification in the soft tissues (especially in the kidneys, lungs and gastro-intestinal tract).⁹⁸ Metastatic calcification was observed in the dogs dying of acute experimental hyperparathyroidism which my colleagues and I examined. When we studied dogs which were suffering from chronic hyperparathyroidism (but which had completely recovered from any acute hyperparathyroidism that may have existed previously), we found metastatic calcification completely or virtually absent at autopsy. We interpreted this as indicating that the metastatic calcifications which probably had been present in these animals earlier were resorbed during the chronic stage of the hyperparathyroidism.

With toxic doses of viosterol the effects are quite similar, but the tendency to calcification of blood vessels seems to be greater than in hyperparathyroidism. Kreitmair and Moll⁹⁹ demonstrated calcium deposits of such degree that the walls of large and small blood vessels were stiff and tubelike. The calcification was most intense in the media, although the other coats may have been involved. With enormous single doses of viosterol, Ham¹⁰⁰ produced in the rat massive calcifications in the aorta, coronary vessels and cardiac musculature as early as forty-eight hours after administration. Shohl, Goldblatt and Brown¹⁰¹ fed doses of viosterol that killed their young rats in from five to fourteen days. They observed parenchymatous degeneration, necrosis, inflammatory infiltration and calcification in various organs (mainly, however, in the tubules and vessels of the kidney, the muscle and vessels of the heart and the muscularis and mucosa of the stomach); calcification appeared with moderate frequency in the lungs and aorta

97. Bross, K.: *Centralbl. f. allg. Path. u. path. Anat.* **49**:229, 1930.

98. Hueper, W.: *Arch. Path.* **3**:14, 1927.

99. Kreitmair, H., and Moll, T.: *München. med. Wchnschr.* **75**:637, 1928.

100. Ham, A. W.: *Arch. Path.* **14**:613, 1932.

101. Shohl, A. T.; Goldblatt, H., and Brown, H. B.: *J. Clin. Investigation* **8**:505, 1930.

but rarely in the suprarenal glands. Roentgenologically, the bones of their rats showed rarefaction of the shafts; microscopically, the ribs showed thinning of both the cortex and the spongiosa. Soeur,¹⁰² working in this laboratory, found that large doses of viosterol demineralized the bones of guinea-pigs, but the resorption was not severe enough to induce great degrees of marrow fibrosis. Grauer,¹⁰³ feeding large doses of viosterol to young guinea-pigs, induced much more severe demineralization, the resorption of bone being associated with considerable marrow fibrosis.

In spite of the fact that, histologically, resorption of the bones (and therefore demineralization) was noted by a number of investigators, Jones and Robson¹⁰⁴ stated that the ash content of the femora of young and old rats given large doses of viosterol was not especially different from that of their controls. Without the least reflection on the correctness of the chemical analyses made by these workers, it should be pointed out that the rat has a special tendency to react to substances like viosterol by the appearance of an osteosclerosis in the metaphyses. Extensive pathologic changes may therefore exist in a bone, with no significant alteration in the ash content, owing to the substitution of new bone for the resorbed bone.

With regard to the metastatic calcification produced by toxic doses of parathyroid extract-Collip or viosterol, the same controversy has arisen as in the case of spontaneous metastatic calcification. This controversy hinges on the same question, as to whether the degeneration of the tissues precedes the deposition of the calcium salts. Ham¹⁰⁰ does not believe that the depositions depend on degenerative changes in the tissues. However, Shohl, Goldblatt and Brown¹⁰¹ found that irritative and toxic processes were associated with the decalcification. They could not be certain whether such changes always preceded the deposition of the calcium salts. In this connection, Shelling¹⁰⁵ stated that the composition of the diet fed to rats, with respect to the calcium and phosphorus content, is a determining factor in the toxicity and hypercalcifying property of viosterol. He found that large amounts of phosphorus in the diet, in the presence of viosterol, render the tissues more susceptible to metastatic calcification. He claimed that rats fed a diet of a high calcium and low phosphorus content and given toxic doses of viosterol may die without evidences of metastatic calcification, although hypercalcemia exists.

The fact that parathyroid extract-Collip and viosterol in toxic doses both produce metastatic calcification, hypercalcemia and hyperphos-

102. Soeur, R.: *Arch. internat. de méd. expér.* **6**:1, 1931.

103. Grauer, R. C.: *Proc. Soc. Exper. Biol. & Med.* **29**:466, 1932.

104. Jones, J. H., and Robson, G. M.: *J. Biol. Chem.* **91**:43, 1931.

105. Shelling, D. H.: *Proc. Soc. Exper. Biol. & Med.* **28**:298, 1930.

phatemia has led to much speculation as to the manner in which they bring about these effects. Taylor, Weld, Branion and Kay¹⁰⁶ held that toxic doses of viosterol accomplish their injurious effects, including calcium metastases, through stimulation of the parathyroid glands. Harris¹⁰⁷ and many others disputed this view, holding that no evidence has been offered in its favor. In fact, it is known that toxic doses of viosterol will produce all of their effects even after extirpation of the parathyroid glands. Taylor and Weld¹⁰⁸ further held that large doses of viosterol depress the power of the intestine to excrete calcium; the calcium which it mobilizes from the bones accumulates in the serum and is excreted through the kidneys. On the other hand, Bauer, Marble and Claffin¹⁰⁹ found that the beneficial effects of therapeutic doses of viosterol are to be attributed to the intake of calcium and not to stimulation of the parathyroids.

106. Taylor, N. B.; Weld, C. B.; Branion, H. D., and Kay, H. D.: *Canad. M. A. J.* **24**:763, 1931.

107. Harris, L. J.: *Lancet* **1**:1031, 1932.

108. Taylor, N. B., and Weld, C. B.: *Brit. J. Exper. Path.* **13**:109, 1932.

109. Bauer, W.; Marble, A., and Claffin, D.: *J. Clin. Investigation* **11**:47, 1932.

(To be Concluded)

Notes and News

Awards.—The honorary degree of doctor of science has been conferred by the Ohio State University on Edward Francis of the National Institute of Health, Washington, D. C.

The Dutch Red Cross Society has awarded its gold medal to Karl Landsteiner, member of the Rockefeller Institute for Medical Research, for his discovery of the blood groups.

Society News.—The American Society of Clinical Pathologists has elected the following officers for 1933-1934: president, A. G. Ford; president-elect, F. H. Lamb; vice-president, J. J. Seelman; secretary-treasurer, A. S. Giordano (South Bend, Ind.).

An International Congress on the Scientific and Social Fight Against Cancer will be held in Madrid, Oct. 25 to 30, 1933, under the auspices of the Spanish League Against Cancer. The secretary is Julio Bejarano, Atocha, 104, Madrid.

A plenary meeting of the Société Anatomique de Paris will be held in Paris on Oct. 12 and 13, 1933. The two subjects for special discussion are cerebral hemorrhage and the medicosurgical anatomy of the nervous peduncles of the visceral apparatus. The secretary is Dr. René Huguenin, 21, rue de l'Ecole-de-Médecine, Paris (VI).

Consent for Necropsy of Child.—A verdict in favor of Harvey S. Thatcher and Albert F. De Groat of the department of pathology in the University of Arkansas has been rendered in the suit against them on account of necropsy on a child. The mother of the child had signed the permit for the necropsy, but the father had not although he was present at the time. Hereafter both parents will be required to sign permits for necropsy, as they are joint guardians under the laws of Arkansas.

Obituary

WILLIAM THOMAS COUNCILMAN

1854-1933

'Dr. Councilman's great great grandfather, Christopher Councilman, came from Holland and settled in Baltimore County, Md., early in the eighteenth century. From him descended the Councilmans and Counselmans of America. His mother was Christiana Drummond Mitchell, of English and Scotch descent. Her father was a lawyer and judge, and her mother, Elizabeth Crane, a daughter of Col. Thomas Crane of the English army.

The Councilmans of Baltimore County were sturdy, energetic and independent farmers, public-spirited and influential in the development of horticulture. Dr. Councilman's father, a graduate in medicine from the University of Maryland, practiced medicine for a few years in Calvert County, Md., in the village of Friendship. In 1852 he moved to Pikeville and settled on part of the family land, about sixty acres, and, like other physicians of that region and period, directed farming operations while engaged in the active practice of medicine. On this farm Dr. Councilman was born on Jan. 1, 1854. There his barefooted boyhood was spent. He fished, hunted and assisted at chores; absorbed interest in horticulture and gardening from his father and mother; acquired respect for agricultural achievement, and above all, a great love for creative gardening, which he practiced throughout his life.

Dr. Councilman's education began at home; at 7 years of age he went to the district school, and at 10 years, to St. Thomas School (Episcopalian), which required a daily three and a half mile tramp each way. In 1867, at the age of 13, he entered the first preparatory class of St. John's College, Annapolis, which he left when 16 years old, at the end of his sophomore year. Stimulated by his brother Charles, he took a position with a firm in the business of importing and jobbing coffee and sugar. Then he had a brief venture by himself in Charlestown with some success, but eventually distaste. Soon, at his father's suggestion, he took up the study of medicine at the University of Maryland, obtaining the degree of M.D. in 1878, still young in years, only 22, but having had unusual contacts with the realities of life.

The opening of Johns Hopkins University and Huxley's address in 1876 made a great impression on him. In the spring before his graduation he came in contact with Henry Newhall Martin, professor of

physiology at Johns Hopkins University, and learned to use a microscope, did work in experimental physiology and saw research in progress.

After graduation, he became assistant quarantine officer of Baltimore. With the first money earned he purchased a microscope, and his work which Martin saw on a visit to the station led to an assistantship in physiology at Johns Hopkins University and participation in the conduction of a course in general biology. The following summer, again at the quarantine station in order to earn money for a trip abroad, he



Photograph by Bachrach

WILLIAM THOMAS COUNCILMAN

1854-1933

made studies on the origins of cells in the inflamed cornea, which won a prize of one hundred dollars offered by the leading medical society of Baltimore. The winter of 1879-1880 was spent at Bay View Asylum. After another summer at the quarantine station he had, in November, 1880, sufficient funds for travel abroad.

At Vienna he was rebuffed by Stricker, who did not like Councilman's statements, contrary to his own, regarding the origins of cells in inflammation. He obtained a place with Chiari for the winter, and in the spring he went to Leipzig and worked with Cohnheim and

Weigert; thence he went to Strassburg and von Recklinghausen. In May, 1882, he returned to Vienna for more work with Chiari and Kaposi. In October, 1882, he returned and obtained a fellowship at Johns Hopkins University, was associated with Sternberg in bacteriologic work, and for the next few years taught in the two medical schools in Baltimore, the Maryland University and the College of Physicians and Surgeons. He performed postmortem examinations at Bay View, and wrote short papers, one with Abbott on malaria and one entitled "The Microscopical Investigation of the Brain and Spinal Cord."

In 1886, he joined Dr. Welch as associate in pathology. In 1888 he went abroad for another year of study in preparation for his appointment as assistant professor of pathology and resident pathologist at Johns Hopkins Hospital. The classic monograph with Lafleur on amebic dysentery published in 1891 is his best known work of this period and is extensively illustrated with drawings made by himself. The years 1889-1892 at Johns Hopkins University brought him into intimate daily association with Welch, Osler, Halsted and Mall.

Dr. Councilman's election as Shattuck professor of pathological anatomy at Harvard University came in 1892. Hitherto Boston and the Harvard Medical School had reared their own professors; the departure from custom was a mark of special distinction and focused attention on him. He probably achieved what was expected of him, for he brought new life into the school. Appointed visiting pathologist to the Boston City Hospital in 1892, he organized the laboratory there and drew Mallory into the field of pathology. Within a year he boldly wrote the trustees of the Massachusetts General Hospital that they needed a pathologic department "with a full time salaried pathologist in charge," and so, when in 1896, a building for the purpose was completed, he recommended James Homer Wright, who became the first "Pathologist and Director of the Clinical Laboratory" of that famous institution.

Perhaps the most important of Councilman's innovations was keeping "open house" in his department. He made opportunities to work in pathology attractive by his enthusiasm and drew to him and into the field of pathology many men now holding professorships in pathology or medicine. He was constantly on the watch in the classroom for students of ability. He fostered the development of Southard and finally the establishment of a separate department of neuropathology.

As a teacher, he was stimulating through his enthusiasm. His lectures were never dull, and were always illuminated by blackboard sketches and enlivened by his whimsical humor. In earlier years the students probably got considerable enjoyment from his explosive enunciation of certain terms such as "polymorphonuclear leukocyte" because

of his tendency to stammering and his fiery determination to overcome it. Life in contact with Councilman was never dull. He married Isabella Coolidge of Boston in 1894, and until his children reached an imitative age, expressions of interest and enthusiasm as well as of anger were apt to be accompanied by very pungent and forcible expletives. At times he would seek companions for a visit to the Art Museum or the Arnold Arboretum which he loved and knew thoroughly, and in the spring of the year for supper and Bock beer, and on holidays, at any season, for walking excursions into the country for pistol practice and lunch of bread, chops and bacon toasted on green sticks over an open fire. He was a "crack shot" with pistol and revolver and practiced with them throughout his life.

His memory was extraordinary, and at sight of an unusual specimen he could refer to helpful articles in *Virchow's Archives* and *Ziegler's Beiträge* by page and volume.

In teaching, he emphasized the laboratory side and endeavored always to improve that part of the course for students. He stressed learning to observe and to do rather than the acquisition of facts.

His most important work at Harvard University was his influence on teaching. His duties as administrator and teacher and in the hospital were constantly heavy, and his list of publications is not a long one. When the Peter Bent Brigham Hospital opened in 1913, he took over the pathologic department with great enthusiasm, even forsaking in the first years his family and beloved gardens at York Village, Me., during part of the summer vacations. For Buck's "Reference Hand Book of the Medical Sciences," he wrote articles on glanders, rhinoscleroma, tuberculosis and inflammation. His best known scientific contributions are a study on nephritis in 1897, an article on epidemic cerebrospinal meningitis with Mallory and Wright in 1898 (a monograph published as a report of the State Board of Health of Massachusetts), an article on diphtheria with Mallory and Pearce in 1900, and the large monograph on the pathology and etiology of variola and vaccinia with Magrath, Brinckerhoff, Tyzzer, Southard, Thompson, Bancroft and Calkins in 1904. This splendid monograph, probably the best ever written on the pathology of smallpox, has not received the credit it deserves. In spite of the wealth of pathologic observations and experimental studies it contains, one finds it too little consulted, probably because of the association in the minds of workers with overemphasis on the inclusion bodies (*Cytoryctes variolae*) of Guarnieri. The real value of the work dropped because of the fall in news value which came with the nonacceptance of *Cytoryctes*.

Dr. Councilman also wrote numerous addresses, one about Osler, the others pertaining to medical education and stressing the importance

of the laboratory methods in teaching. With F. B. Mallory he wrote a "Syllabus of Pathology," published in 1904 by J. L. Fairbanks Company of Boston. Later he wrote a larger volume, "Pathology, A Manual for Teachers and Students," published in 1912 by W. M. Leonard of Boston. "Disease and Its Causes" was published in 1913 as one of the series of The Home University Library of Modern Knowledge by Holt and Company.

He was a member of the Council on Medical Education of the American Medical Association from 1904 to 1909, and a member of the Board of Trustees from 1909 to 1917.

In 1916 Dr. Councilman and Dr. R. H. Lambert went as medical observers up the Amazon River with Dr. A. Hamilton Rice's expedition. The medical report of the expedition, which appeared in 1918, reproduces many photographs by Dr. Councilman, and reveals that he was as much interested in the forests as in the diseases of the human inhabitants of the regions traversed.

He returned from the expedition with impaired health and thereafter suffered from attacks of angina, which in no way seemed to depress him or diminish his enthusiasms over his favorite interests and hobbies. In 1917, because of the retiring age of 63, he left the Brigham Hospital. In 1919 he went to Pekin, accompanied by Mrs. Councilman, as temporary professor of pathology at the Union Medical College. There he remained for two enjoyable years. He resigned from his professorship at the Harvard Medical School in 1923. His last scientific interest was in the symbiotic fungi in root hairs of plants and trees. In the few years before his retirement from teaching and for several years afterward a microscope accompanied him always when he was traveling. A friend once surprised him over a microscope studying root hairs in the band-stand in a park in Los Angeles. His final paper, published in the Proceedings of the National Academy of Science in 1923, was entitled "The Root System of *Epigaea Repens* and Its Relation to the Fungi of the Humus."

During the last ten years of his life he lived during the growing seasons at York Village, Me., where every tree, vine, shrub and plant on his place had been planted by him. He worked in his gardens up to the day of his death. A legacy from him which will be long cherished is about six hundred yards of iron paling fence on the Van Dyke Street side of the Peter Bent Brigham Hospital which he personally planted with his favorite climbing roses soon after the hospital buildings were erected.

One never knew how much Dr. Councilman cared about honors. That he enjoyed the opportunities for effective service offered by the presidency of the board of trustees of the American Medical Association was quite evident. A large gold medal given to him by some society

has for years reposed in a desk in a storage warehouse. None of his colleagues ever heard Dr. Councilman mention the honor. He was a fellow of the American Academy of Arts and Sciences, fellow of the Philosophical Society of Philadelphia and member of the National Academy of Sciences. His honorary degrees were A.M., Harvard University, 1899; A.M., Johns Hopkins University, 1902; LL.D., University of Maryland, 1907; LL.D., McGill University, 1911; LL.D., Western Reserve University, 1929; LL.D., St. John's College, 1932.

He is survived by Mrs. Councilman and three daughters, Mrs. W. O. Morgan and Mrs. Frank Wigglesworth, both of Cambridge, Mass., and Dr. Elizabeth Councilman, a graduate of Columbia University College of Physicians and Surgeons and now of Bellevue Hospital, New York.

Dr. Councilman was a sturdy, kindly, observant character. He practiced the amenities of life unadorned by formalities or artificialities. His personality stood naked before all. He cultivated neither reserve nor mannerisms; he achieved dignity unconsciously by virtue of directness, competence and honesty. In his pupils he inspired respect and admiration and in the highest degree, affection. He understood the nature of man as thoroughly as he understood trees, and his appraisal of men was rapid, accurate and tolerant, because he expected faults, particularly selfishness of which he was so free. His sources of satisfaction were many: in affectionate family life, in achievement in work and in recreative fields and in the progress of men to whose careers he gave impetus.

S. B. WOLBACH, M.D.

Abstracts from Current Literature

Pathologic Anatomy

CARDIAC HISTOPATHOLOGY IN THYROID DISEASE. C. V. WELLER, R. C. WANSTROM, H. GORDON and J. C. BUGHER, *Am. Heart J.* 8:8, 1932.

A morphologic study of the hearts of thirty-five patients with exophthalmic goiter showed, with but few exceptions, no gross or microscopic pathologic changes not equally represented in a carefully matched control series. The exceptions found were: (1) a relatively higher incidence of myocardial fibrosis, endocardial sclerosis and cellular infiltrations in the series with exophthalmic goiter, and (2) one case in the series of thirty-five which showed an active focal myocarditis in which no etiologic factor could be ascertained other than the hyperthyroid state. Twenty-eight, or 80 per cent, of the exophthalmic series showed areas of myocardial fibrosis, as compared with 51.5 per cent of the control series. It is impossible to determine to what extent, if any, such areas of fibrosis may be the result of an active myocarditis of the type found in the single case. The hearts of fifty-five patients with adenomatous (nodular) goiter failed to show any significant difference in the incidence of pathologic changes as compared with a matched nongoitrous control series.

AUTHORS' SUMMARY.

THE HEART IN OLD AGE. FREDRICK A. WILLIUS and HARRY L. SMITH, *Am. Heart J.* 8:170, 1932.

This study of the heart comprised 381 patients, ranging in age from 70 to 99 years, who came to necropsy; 59.4 per cent of the patients were between the ages of 70 and 74, whereas 15.7 per cent were 80 years or older. There were five men to one woman. Varying degrees of coronary sclerosis occurred in all cases, but the involvement was moderate to advanced in 72.5 per cent. Likewise, aortic sclerosis was a constant finding, but existed in from moderate to marked degree in 80 per cent of the cases. Sclerosis of the valves occurred in 92.7 per cent. Cardiac disease other than arteriosclerosis was present in 16.4 per cent of the cases. The blood pressure in 371 cases indicated a tendency toward hypertension. The cause of death in this group of aged patients were diverse. Only 12.6 per cent died of heart disease. This clearly shows the suitability of the material for a study of this nature.

AUTHORS' SUMMARY.

MEDIASTINAL ENLARGEMENT IN ACUTE LEUKEMIA. JEAN V. COOK, *Am. J. Dis. Child.* 44:1153, 1932.

The cases of nine boys with massive leukemic enlargements of the thymic region are reported. All died of acute leukemia, although clinical evidences of mediastinal tumor were noted in four before the development of a leukemic blood picture. Postmortem examination in two cases revealed large lobular masses in the thymic areas, which microscopically did not present normal thymic elements, but were made up of mononuclear leukemic cells (probably myeloid) held together by connective tissue stroma. Extensive infiltration by similar cells was seen in the liver, kidneys, spleen and other tissues. All lymphoid structures were moderately enlarged and infiltrated with the leukemic cells. A review of eighty-three cases, including the nine not previously reported, shows that the condition affects males almost six times as frequently as females, and that over 90 per cent occurred in persons under 30 years of age. The mediastinal mass is probably the result of leukemic cells carried there by the blood stream rather than a true neoplastic tumor arising in situ.

RALPH FULLER.

CONGENITAL DEFECT OF THE SKIN IN A NEW-BORN INFANT. VERNON BOOTH DOWLER, *Am. J. Dis. Child.* **44**:1279, 1932.

In consideration of the two lumbar defects, attention is directed to the dimpled "depressions" so often seen in the routine examinations of groups of children of all ages. These so-called "dimples" are usually seen more frequently at the following sites: at the acromion eminences at the shoulder, over the olecranon at the elbows and at the posterior superior iliac spines. The premise is offered at this time that these dimples represent completely healed areas of congenital cutaneous defect. Again, the suggestion is made that, in view of the deep grooving of the defects of the leg, the so-called amniotic grooves that have been noticed not infrequently on the lower extremities of children may be, in reality, totally healed cutaneous defects. It is also evident from a study of this case that the term congenital cutaneous defect should obviously include loss of subcutaneous tissue.

AUTHOR'S SUMMARY.

GLOMERULAR LESIONS ASSOCIATED WITH ENDOCARDITIS. E. T. BELL, *Am. J. Path.* **8**:639, 1932.

Two forms of glomerulitis, namely, diffuse and embolic, are found in association with endocarditis. Diffuse glomerulitis was found with the various types of endocarditis as follows: acute rheumatic, 22.2 per cent; acute primary bacterial, 28.6 per cent; subacute bacterial, 64.8 per cent, and secondary acute, 33.3 per cent. It is characterized by an increase in the number and size of the endothelial cells and often by thickening of the capillary basement membrane. The extent of capillary obstruction is usually much less than in clinical acute glomerulonephritis, but in seven instances of subacute endocarditis glomerulitis had reached the clinical level. Diffuse glomerulitis bears some relation to the intensity and duration of septicemia. Embolic or focal glomerulitis was found in the different forms of endocarditis as follows: acute rheumatic, 2.9 per cent; acute primary bacterial, 7.1 per cent; subacute, 52.8 per cent, and secondary acute, 5.8 per cent. In one instance there was no endocarditis. Two distinct types of embolic lesions occur, the fresh hyaline and the fibrous. The fresh hyaline lesion in its simplest form is a capillary thrombosis, and all the smaller lesions are readily recognized as such. The larger lesions are composed of many thrombosed capillaries, which may be identified until the capillary walls have undergone necrosis. The hyaline lesion is not an infarct but a thrombosis and necrosis of capillaries resulting from the lodgment of bacteria. The necrotic portion of the glomerulus disintegrates and disappears. The fibrous lesion is a reaction characterized by a marked growth of the basement membranes of the capillaries. The thickened membranes obliterate the capillaries and give the glomerulus a fibrous structure. The fibers are formed entirely from basement membranes; there is no invasion by fibroblasts from without. The fibrous lesion, like the fresh hyaline, may involve one or more lobules or the entire glomerulus. It develops independently of the fresh hyaline lesions. In subacute bacterial endocarditis there were fifteen instances of severe renal insufficiency, of which five were due to embolic glomerulonephritis, seven to acute glomerulonephritis and three to chronic glomerulonephritis. The fresh hyaline embolic lesions develop earlier than the fibrous, and may be found at any time during the course of the disease. The frequent absence of embolic lesions in typical clinical examples of subacute bacterial endocarditis has not been explained. Diffuse glomerulitis is frequently found in association with embolic lesions. Epithelial crescents frequently cause atrophy of the glomerular tufts by compression. Fibers form between the epithelial cells and convert the crescent into a dense fibrous structure. These fibers are of epithelial origin. In the glomeruli, fibers which later give the staining reactions of collagen are formed from three distinct sources: intracapillary fibers from the endothelial cells, fibers formed from thickened capillary basement membranes and fibers formed by the epithelial cells of the crescents.

AUTHOR'S SUMMARY.

GLOMERULAR CHANGES INDUCED BY URANIUM NITRATE, MERCURIC CHLORIDE AND POTASSIUM BICHROMATE. W. C. HUNTER and J. M. ROBERTS, *Am. J. Path.* 8:665, 1932.

By a special staining method (azocarmine) distinct changes, interpreted as evidences of injury, can be demonstrated in the glomerular basement membrane of kidneys damaged by uranium nitrate, mercuric chloride and potassium bichromate. The lesions in the basement membrane are purely degenerative in character, are present in both acute and chronic stages of chemical nephropathies and appear to be permanent. The renal glomerulus is more vulnerable to poisons than the tubules, and fails to develop the same degree of increased resistance toward them. The opinion is advanced that alterations in the basement membrane of the type described may play an important rôle in the renal disturbances induced by certain metallic salts. Fibrosis and connective tissue hyperplasia are not responsible for the appearance of the glomeruli in chronic uranium and sublimate nephropathies. The existence of other long recognized glomerular changes demonstrable with ordinary stains is affirmed. Uranium nitrate and mercuric chloride produce more histologic alterations in the glomeruli than potassium bichromate.

AUTHORS' SUMMARY.

CYSTIC NECROSIS OF AORTIC MEDIA. A. R. MORITZ, *Am. J. Path.* 8:717, 1932.

Three cases of spontaneous rupture of the aorta with cystic necrosis of the media have been described. The necrosis developed focally in areas that were the seat of chromatropic or mucinous degeneration, and was not associated with any significant intimal change or inflammatory reaction. These cases have been compared with the previously reported cases of this disease, and certain additional observations made. Tearing of the elastic elements occurred with and without cystic change, and neither the cystic change nor the elastic tears were limited to the ascending arch of the aorta. The lesions were qualitatively similar to those commonly seen in sclerotic aortas, and differed in that the necrotic foci were larger and exhibited a greater tendency to repair. In the cases reported to date evidence of hypertension has been common but not constant, and in a considerable number the rupture has occurred while the patients were at rest. Additional studies will be profitable in establishing the similarity or dissimilarity of this disease to the changes commonly seen in arteriosclerosis without advanced intimal lesions.

AUTHOR'S SUMMARY.

COMMON MESENTERY WITH INTESTINAL OBSTRUCTION. A. R. MORITZ, *Am. J. Path.* 8:735, 1932.

Four cases of mesenterium commune have been described, one in an infant manifesting no disturbance referable to the anomaly, and three in infants who died of intestinal obstruction secondary to the hypermotility engendered by the defective mesenteric attachments. In two of the infants, the obstruction was caused by a volvulus of 360 degrees in a clockwise direction, which, because of the abnormal motility of the terminal portion of duodenum, reversed not only the planes of the small and large intestine but also the relation of superior mesenteric artery to the duodenojejunal segment of the intestine. The condition in these two cases was such as to stimulate reversed developmental rotation. These cases illustrate the surgical necessity of determining at the outset whether the condition is a real reversed rotation or a secondary volvulus due to defective fixation. If a correction of a true reversed rotation established during the third month of fetal life is made, one must regard the reversal as normal for that person, while only the volvulus type may be reduced by a return to the normal position.

AUTHOR'S SUMMARY.

FIBROCYSTIC DISEASE OF THE BONES WITH TUMOR OF A PARATHYROID GLAND. R. S. ROSEDALE, *Am. J. Path.* **8**:745, 1932.

The literature concerning the development of the concept of the relation of generalized fibrocystic disease of bones to hyperparathyroidism has been reviewed. A case of generalized fibrocystic disease of the bones with a tumor of the parathyroid gland has been presented.

AUTHOR'S SUMMARY.

THE STRUCTURE OF THE THYROID IN THE NEW-BORN. V. I. KRINSKAJA, Frankfurt. *Ztschr. f. Path.* **43**:41, 1932.

Contrary to the results of other research, colloid substances were found frequently in the thyroid in the new-born. In only three of the fifty thyroids examined was colloid missing. Fully developed follicles were regularly present. The author, whose material was taken from Baku, Russia, states that at present she is unable to explain the discrepancies between her findings and those reported by western European investigators.

AUTHOR'S SUMMARY.

TERTIARY SYPHILIS OF THE LIVER IN CHILDREN AND ITS RELATION TO CIRRHOSIS. U. PETERSEN, Frankfurt. *Ztschr. f. Path.* **43**:44, 1932.

The clinical diagnosis of the condition of a 4 year old girl was syphilitic cirrhosis of the liver. The postmortem diagnosis was lobulated syphilitic liver, enlarged spleen, lipid nephrosis, ascites and purulent peritonitis. Even though no spirochetes were found in the liver, the diagnosis of lobulated syphilitic liver was made because of the coarse granular appearance, a productive inflammation starting from the capsule and extending into the periportal spaces, while the liver tissue in general was well preserved. Also, the lipid nephrosis seemed consistent with syphilis. Clinically, there was a typical saddle nose, and the Wassermann reaction was positive when the child was first seen. In reviewing the literature critically, the author did not become convinced of the existence of a true syphilitic cirrhosis.

O. SAPHIR.

DIFFERENTIAL DIAGNOSIS OF GENUINE ATROPHY OF THE LIVER AND ACUTE PHOSPHOROUS POISONING OF THE LIVER. H. KUBO, Frankfurt. *Ztschr. f. Path.* **43**:56, 1932.

Six cases of acute phosphorus poisoning came under observation, death occurring in from seven hours to five days. The liver of the patient who died seven hours after having taken two tubes of "phosphorus paste" (used for rat poisoning) revealed necrotic foci within the acini without definite appearance of fat in the liver. The same observation was made on rabbit's livers, the rabbits dying from three and one-half to four and one-half hours after having been poisoned with phosphorus paste. Because of the fact that fatty metamorphosis of the liver always is taken as an indication of phosphorus poisoning, in differentiating this condition from genuine (yellow) atrophy of the liver, no significant fat, however, being present in the livers of the patients dying shortly after phosphorus poisoning, the author concludes that no strict differentiation of these two diseases of the liver can be made grossly or histologically.

O. SAPHIR.

A RARE MALFORMATION OF THE CORONARY VESSELS. I. LÖWENHEIM, Frankfurt. *Ztschr. f. Path.* **43**:63, 1932.

Both coronary arteries originated normally. The first portion of the right coronary artery up to a point about 2 cm. from its mouth was of normal width.

Beginning from there, the lumen of this artery abruptly became much wider, measuring about 6 cm. in circumference. The dilated portion extended up to the region of the septum. At first glance, it seemed as if the dilated portion would end blindly. Close inspection, however, revealed that a small communication existed between the dilated end-portion of the right coronary artery and the right coronary vein. The latter also revealed a normal orifice and first portion. Its distal portion, however, which communicated with the distal portion of the right coronary artery, also was markedly dilated. Microscopically, neither the sections taken from the artery nor those from the vein showed significant changes.

O. SAPHIR.

DIFFUSE SCLEROSIS (LEUKENCEPHALITIS SCLEROTICANS). J. CASPER, Frankfurt. Ztschr. f. Path. 43:69, 1932.

A 34 year old man, a diabetic patient who four months before admission to the hospital was ill with pneumonia, complained of headache, dizziness, vomiting, changes in the ocular muscles, and right-sided paresis. The cerebrospinal fluid was sterile on bacteriologic examination. The white blood count revealed 15,100 cells. The temperature rose to 39.5 C.; the patient became somnolent, and died six days after admission. The clinical impressions were: possible encephalitis; Schilder's disease, and tumor of the region of the pons (abscess?). Postmortem examination of the brain revealed a large, not well defined area corresponding to the hemisphere of the left occipital lobe, in which there was a marked loss of myelin sheaths combined with a proliferation of glia. A few such foci were also present in the pons. The cortical portion of the brain and the basal ganglia revealed no changes. Nowhere did the proliferation of the glia assume tumorous growth. The capillaries were dilated in the marginal portions of these areas, and some of the vessels were surrounded by round cells. The author believes that the changes in the brain were the result not of bacterial invasion but of bacterial toxins.

O. SAPHIR.

THE GLIA REACTION IN ACUTE INFECTIONS AND INTOXICATIONS AND FOLLOWING ROENTGEN TREATMENT. B. N. MOGILNITZKY and W. S. RJASANOWA, Frankfurt. Ztschr. f. Path. 43:114, 1932.

The material used for this study was taken from forty-four cases of sepsis, pneumonia, erysipelas, tetanus, diphtheria, scarlet fever, anthrax infections, alcohol and opium poisoning, eclampsia and uremia. In twenty instances, rabbits were exposed to roentgen radiation, and in three instances rats were poisoned with opium. Also, a series of dogs were exposed to roentgen radiation. The author states that in cases of acute infectious diseases and intoxications, and as a result of roentgen treatment, a proliferation of Hortega's elements, and of apolar glia fibers with an increase of the oligodendroglia occurs. In many infectious diseases, the microglia is exposed to destructive changes. No relation could be found between an increase of Hortega's elements and the degree of changes of the ganglion cells. The proliferation of microglia forms the morphologic basis for the so-called encephalopathies and "occult" infections of the brain. The function of astrocytes, Hortega's elements and the apolar glia is discussed.

O. SAPHIR.

RUPTURE OF THE AORTA OF TUBERCULOUS ORIGIN. G. HABÁN, Frankfurt. Ztschr. f. Path. 43:175, 1932.

A 27 year old man, whose right kidney and both epididymes were removed because of tuberculosis, suffered from hematemesis and marked anemia. The clinical diagnosis was gastric ulcer. He died after an attack of hematemesis. At autopsy, a tuberculous ulcer of the aorta was found, which had perforated into the esophagus. There was miliary tuberculosis of the lungs, spleen, liver and left kidney, in addition to old calcified tuberculosis of the hilus nodes of the lungs

and scars on the apex of the right lung. The author believes that the rupture of the aorta was not the result of the presence of tuberculous granulation tissue in the media, but was caused by necrosis of the media which in turn might have been the result of toxins of the tubercle bacilli or, possibly, of thrombosis of the vasa vasorum.

O. SAPHIR.

THE SPLEEN IN CASES OF ILEUS. T. ROMSAUER, Frankfurt. *Ztschr. f. Path.* **43**: 184, 1932.

There are no specific changes in the spleen grossly or histologically, from which the presence of an ileus may be inferred. The histologic changes resemble those found in so-called septic spleens.

O. SAPHIR.

CONGENITAL DEFECT OF THE TIBIA. C. ALETTER, Frankfurt. *Ztschr. f. Path.* **43**: 196, 1932.

The right tibia was missing. The left proximal portion of the left tibia was normal, but its distal portion was abnormally developed. Both patellae were absent. There also were malformations in both ankle joints.

O. SAPHIR.

PATHOGENESIS OF RACHITIS AND CLINICAL OBSERVATIONS. L. LOEFFLER, Frankfurt. *Ztschr. f. Path.* **43**:231, 1932.

An attempt is made to explain rachitic skeletal changes on the basis of pathologic anatomy and comparative pathology. The author concludes that in rachitis there are a quantitative and a qualitative change in the structure of the bones. The quantitative change is the cause of the qualitative change, the essential of which is the decrease of the calcium content of the bones. The disturbance of the calcium metabolism is secondary. Because of the fact that severe respiratory disturbances, such as bronchiectasis and pneumonia, may be present in patients with rachitis, they should not be overlooked clinically. Sometimes they may be considered the cause of death in patients with rachitis.

O. SAPHIR.

ROUND CELL INFILTRATIONS WITHIN THE SUPRARENALS. J. Soôs and E. RUSZKÓ, Frankfurt. *Ztschr. f. Path.* **43**:340, 1932.

Round cell infiltrations were never found in the suprarenal cortex of infants and of young Hungarian pigs. They neither constitute normal findings nor are present congenitally. They may be present in cases of intoxication, of infectious disease and of any diseases which may heal without leaving remnants. Even though they are sometimes found in cases of sudden death, it is more likely that they represent the result of a slowly developing chronic disease within the suprarenals, and, therefore, they should not be brought in correlation with an acute disease. The author believes that small hemorrhages, necrosis of cortical cells or lipid changes produce a round cell infiltration. The most common location of such round cell infiltrations is the zona reticularis. Their purpose is the carrying away of cellular debris, but they cannot be regarded as blood-forming foci.

O. SAPHIR.

SUPRARENAL HEMORRHAGE. A. KRAUS, Frankfurt. *Ztschr. f. Path.* **43**:372, 1932.

Hemorrhages of the suprarenals may cause in rare instances a hemorrhage into the loose connective tissue around the kidneys. Perforation of such hemorrhages into the abdominal cavity in the adult is rare in contradistinction to such perforations in the new-born. Repeated hemorrhages into the suprarenals might occasionally form large bloody cysts. Small hemorrhages often constitute an

incidental finding, but larger hemorrhages into both suprarenals are fatal. Clinically, patients suffering from hemorrhages into both suprarenals reveal a pseudo-peritonitic complex of symptoms (abdominal pains and rigidity, intestinal spasms, obstipation, and vomiting). Such clinical findings, which are explained at autopsy by hemorrhage into both suprarenals, however, are not common. The pathogenesis of such hemorrhages is not fully understood at the present time. It is possible that the peculiar structure of the suprarenal vein constitutes a factor in the explanation of these hemorrhages.

O. SAPHIR.

PERIARTERITIS NODOSA OF THE KIDNEY. A. HINRICHS, *Virchows Arch. f. path. Anat.* **280**:51, 1931.

In generalized periarteritis nodosa the kidney is frequently involved. Grossly, the renal involvement presents nothing characteristic; the kidney is usually scarred by areas of healed infarction, or it may be a large red or large white kidney. In the case reported by Hinrichs, the kidneys were especially involved and on the cut surface revealed innumerable small nodules in the cortex and medulla. The nodular character was due to the lesions of periarteritis nodosa. There were no recent or older areas of infarction.

O. T. SCHULTZ.

DISSEMINATED "MEDIONECROSIS" OF THE AORTA. M. CELLINA, *Virchows Arch. f. path. Anat.* **280**:65, 1931.

A histologic study of a hitherto undescribed form of necrosis of the media of the aorta is presented. Previously recognized forms of necrosis of the media are the idiopathic necrosis associated with spontaneous rupture of the aorta and a mucoid degenerative necrosis which also leads to rupture. The form of necrosis described was encountered in the routine examination of the aortas of elderly persons. This led to a systematic histologic examination of the aortas of ten persons from 71 to 95 years old. The aortas selected were free of calcifying atherosclerosis. Multiple disseminated areas of necrosis were found in every case. The lesions were most numerous in the arch; they were not entirely absent in the thoracic and abdominal aorta. The necroses occurred in the form of streaks from 1 to 10 mm. long that ran parallel to the inner surface of the aorta. They were most numerous in the region of the internal elastic lamella and in the inner third of the media. Characteristic of the areas of necrosis is the complete absence of nuclei and of nuclear remnants in them. A previous increase of elastic and fibrous tissue could be detected in most of the necroses; in a senile atherosclerotic aorta examined for purposes of comparison, the necroses described bore no relation to the atheromatous areas. The cause of the necrosis is not known, but may be a toxic agent that is universally operative in elderly people. In most of the aortas with the disseminated necroses there were seen also minute nonnecrotic areas from which nuclei had disappeared; such areas may be the precursors of the necroses.

O. T. SCHULTZ.

LOCALIZED THICKENINGS AND POCKETS OF THE ENDOCARDIUM. I. M. WERTKIN, *Virchows Arch. f. path. Anat.* **280**:87, 1931.

The author describes eight hearts with localized, ridgelike areas of thickening of the endocardium and pocket formation. The thickening of the endocardium is brought about by hyperplasia of the inner layer of the endocardium. It is due not to inflammation but to the mechanical impingement of the blood stream against the endocardium. The formation of Zahn's endocardial pockets is secondary to the formation of the area of thickening and is due to the same mechanical factors. The structures discussed are situated most often on the septal surface of the left ventricle, just below the aortic valve. When the opening of the pocket is directed upward, it is usually due to the regurgitating stream of blood in aortic insufficiency. When the opening is directed toward the apex of the ventricle, it is due

to a combination of diastolic backflow and systolic pressure. In two hearts, the unusual localization of the pocket in one case and the unusual form of the pocket in the other could not be explained by any of the accepted theories. The author is also unable to furnish an explanation of the presence of smooth muscle in some of the structures described by him. There is no analogy between the formation of endocardial pockets and of the semilunar valves, and the formation of pockets is not a purposeful functional adaptation.

O. T. SCHULTZ.

RING-SHAPED THICKENING OF THE ENDOCARDIUM WITH VALVELIKE POCKETS.

K. WOLFF, *Virchows Arch. f. path. Anat.* **280**:107, 1931.

A heart with vegetative aortic endocarditis, the clinical manifestations during life being those of aortic stenosis, presented a ring-shaped thickening of the endocardium of the upper part of the left ventricular surface of the septum. The area of thickening extended onto the posterior surface of the anterior segment of the mitral valve; except for the thickening, there were no inflammatory or other changes on this surface of the valve. From the ring-shaped area of thickening there had been formed a series of small, valvelike pockets the openings of which were directed toward the apex of the heart. Histologic examination revealed no inflammatory reaction in the structure described. Smooth muscle fibers were seen at the base of the pockets. Wolff ascribes the thickening to mechanical factors, and the formation of the pockets to the action of the systolic pressure in a diastolic backflow. The structure could have no useful function.

O. T. SCHULTZ.

TRAUMATIC EPIDERMAL CYSTS. A. BEHRENS, *Virchows Arch. f. path. Anat.* **280**:145, 1931.

The author presents a brief discussion of traumatic epidermal cysts, which occur usually on the palmar surface of the hand or the flexor surface of the fingers. He describes three such cysts. In one, the trauma led to the formation of secondary cysts from an original misplacement cyst that had been present for many years. In another, the trauma led to fracture of a phalanx and to misplacement of epithelium into the bone, where the cyst developed. In the third, the cyst developed in close proximity to the terminal phalanx and led to pressure atrophy and disappearance of bone.

O. T. SCHULTZ.

LOCALIZED GLIOSIS OF THE MEDULLA. G. POMMER, *Virchows Arch. f. path. Anat.* **280**:205, 1931.

In a man who for six years before death had been afflicted with paralysis of the left upper and lower extremities, paralysis of the right side of the face and anesthesia in the distribution of the third branch of the left fifth nerve, microscopic examination of the brain stem revealed a sharply circumscribed area of gliosis that had replaced the tissues of the region of the right olivary body. In a less sharply defined manner the area extended upward and involved the nuclei of the sixth and seventh nerves and the fiber tract of the fifth nerve of the right side. The lesion resulted from vascular obliteration.

O. T. SCHULTZ.

PROSOPOTHORACOPAGUS. O. WALBAUM, *Virchows Arch. f. path. Anat.* **280**:275, 1931.

The monstrosity described is compared with previously reported similar ones and with six thoracopagi studied by the author. The main feature that distinguishes double monsters with fusion of both face and thorax from those with fusion of the thorax alone is the single pharynx, esophagus and stomach of the former.

O. T. SCHULTZ.

CONGENITAL DIVERTICULUM OF THE CECUM. B. ODQVIST and T. PETRÉN, *Virchows Arch. f. path. Anat.* **280:581**, 1931.

After a brief discussion of some of the more unusual forms of congenital diverticulum of the intestine, the authors present a description of a diverticulum of the cecum that was observed by chance during necropsy on a 3 year old girl. A typical Meckel's diverticulum was situated 90 cm. above the ileocecal valve. The appendix was given off from the cecum in the normal position. Arising in the angle formed by the junction of the ileum with the large bowel was a blind diverticulum 6 cm. long by 2.5 to 3 cm. in diameter. It possessed a mesentery in common with the appendix. Its lumen communicated with that of the intestine. Its wall was composed of a mucosa, submucosa, inner muscular coat and external muscular coat. The authors do not consider the structure a reduplicated appendix or a bifurcated cecum, but a congenital diverticulum of the cecum.

O. T. SCHULTZ.

HISTOPATHOLOGY OF THE INTESTINE IN ANKYLOSTOMIASIS. W. ROTTER, *Virchows Arch. f. path. Anat.* **280:587**, 1931.

This work comes from Costa Rica. The usually described acute lesions of ankylostomiasis are small areas of hemorrhage in the submucosa of the upper part of the small intestine, beneath the depths of the folds of the mucosa, where the worms have attached themselves by their hooklets. The traumatic hemorrhage is followed by necrosis and leukocytic infiltration, due to toxic action. In healing, these lesions are transformed into localized fibrous plaques that contain hemosiderin. There occur also minute hemorrhages limited to the mucosa and leukocytic infiltration limited to the stroma of a few villi. These reactions are due to the toxic action of the parasite. As a chronic lesion, the author describes diffuse fibrosis and thickening of the submucosa, over which the mucosa may be fairly normal but is more often thin and atrophic. It is to these chronic lesions that the author ascribes the persisting anemia and cachexia of the infestation.

O. T. SCHULTZ.

A CASE OF APLASIA OF THE CEREBELLUM. N. K. LYSSENKOW, *Virchows Arch. f. path. Anat.* **280:611**, 1931.

Because of the rarity of cerebellar aplasia in adults this gross and microscopic study of the brain is presented, although the clinical history and a protocol of the necropsy could not be found. It is known only that the specimen was from a man who reached the age of 25 years, that he was said to have been psychically normal, and that he had never walked. The vermis of the cerebellum and all its structures were absent. The lateral lobes were much smaller than is normal. They revealed the normal topography, but all the structural elements were quantitatively greatly reduced. The nuclei and tracts of the brain stem that have no direct connection with the cerebellum were normal.

O. T. SCHULTZ.

VASCULAR CHANGES IN CHRONIC LIGNEOUS THYROIDITIS (RIEDEL'S STRUMA). F. ROULET, *Virchows Arch. f. path. Anat.* **280:640**, 1931.

In three thyroids that were the seat of the chronic inflammatory process usually associated with Riedel's name, the author describes vascular changes much more marked than have hitherto been noted. The process involved chiefly the smaller and terminal veins; in one case the small arterioles were also involved. The original tissue elements of the wall of the vein were separated by a cellular granulation tissue that penetrated the wall from the adventitia. The infiltrating tissue was rich in plasma cells. The tissue may penetrate the intima and grow

into and occlude the lumen without thrombosis. Disappearance of plasma cells and lymphocytes and collagenous transformation of the stroma may transform the vessel into a nodule the original vascular character of which is not recognizable. The vascular lesion is suggestive of syphilis, but the author does not consider the process syphilitic.

O. T. SCHULTZ.

DEVELOPMENT ANOMALIES ASSOCIATED WITH ABSENCE OF THE CAUDAL END OF THE VERTEBRAL COLUMN. A. FELLER and H. STERNBERG, *Virchows Arch. f. path. Anat.* **280**:649, 1931.

The authors give a detailed account of the conditions found in two monstrosities of the symphys apus type and compare them with the conditions found in two other monstrosities with maldevelopment of the lower extremities. Maldevelopments associated with defects of the lower end of the vertebral canal they classify as monopus, sirenoid monopus and siren. The term monopus they would reserve for the anomaly in which the vertebral defect is asymmetrical and involves one side only, leading to the failure of development of one posterior limb. Sirenoid monopus they would apply to the monstrosity in which the asymmetrical defect involves also the midportion of the lower vertebral column. Siren is applied to the anomaly associated with a median and bilaterally symmetrical vertebral defect. The absence of the allantois and of one umbilical artery in sirens indicates the very early stage of embryonic development during which the maldevelopment arises. The latter is not due to fusion of two limbs or regression of one limb bud or to external factors, but is due to factors inherent in the germ plasm which result in the lack of formation of sufficient tissue for two limb buds.

O. T. SCHULTZ.

PLICATION OF DIAPHRAGMATIC PLEURA WITH ABNORMAL LOBATION OF LUNG. H. TESSERAUX, *Virchows Arch. f. path. Anat.* **280**:693, 1931.

The anomaly described occurred in a 7 month old boy who died of sepsis of otitic origin. The right pleural cavity was incompletely divided into two portions by a fold of the diaphragmatic pleura that grew upward along the vertebral column, and that divided the lower lobe of the lung into a smaller posterior lobe and a larger anterior portion. A normal middle lobe had not been formed. This unusual anomaly, of which the author could find only three previously reported examples, was ascribed by H. Eppinger, who reported the first case in 1902, to abnormality in the course of diaphragmatic vessels. Tesseraux holds that the anomaly is due to maldevelopment of the embryonic pleuroperitoneal membrane. In the four cases thus far described, the anomaly has been on the right side.

O. T. SCHULTZ.

FUSED DOUBLE MONSTROSITIES AMONG MAMMALS. ELSBET ENGEL, *Virchows Arch. f. path. Anat.* **280**:706, 1931.

Six cephalothoracopagi are pictured and described. These were distributed among four species as follows; hog, two; rabbit, two; dog, one, and lamb, one.

O. T. SCHULTZ.

CEREBRAL INJURY IN NEW-BORN CHILDREN CONSEQUENT ON BIRTH TRAUMA; WITH AN INQUIRY INTO THE NORMAL AND PATHOLOGIC ANATOMY OF THE NEUROGLIA. ERIK RYDBERG, *Acta path. et microbiol. Scandinav.*, 1932, supp. 10, p. 1.

In the human fetus the glia to a large extent forms a syncytium. The evidence points to its ectodermal origin. In the new-born fatty substances accumulate normally about glia cells and their expansions. These fatty substances may form

material for the myelinization of nerve fibers. The regressive changes in the glia and nerve fibers in injuries to the brain in the new-born are essentially of the same nature as those that occur in injuries to the brain later in life. The nerve fibers are more resistant than the fetal glia, which readily undergoes softening. Phagocytic fat granule cells may come from different sources. That intracranial hemorrhages in the new-born so frequently are multiple indicates that they are due to general disturbances of the intracranial circulation in the course of birth, but local vascular injuries may occur also as in tentorial tears. In seventy-five new-born infants, gross intracranial hemorrhage, by far most commonly meningeal, occurred in fifty-eight; hemorrhage into the brain tissue or ventricles was found in twenty-eight of the seventy-five cases. Subependymal hemorrhages are characteristic of premature fetuses. Microscopic capillary hemorrhages are almost constant in the new-born. In thirty-four new-born infants with major cerebral symptoms, considerable intracranial hemorrhage accompanied by softening was found in all except six cases in which degenerative changes were present. Cases of brain trauma in birth may run their course without symptoms. Account is given of necropsies in forty-eight instances in which there were major cerebral symptoms during the first few days of life followed by survival for one year or longer. Only nine of these infants could be grouped as normal; one-third were classed as idiots or imbeciles; the mentally retarded numbered ten, and there were nineteen epileptic infants. In the chapter on treatment the value of the injection of blood (universal donor) into the superior longitudinal sinus is emphasized.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

BEHAVIOR OF BACTERIOPHAGE IN BODY FLUIDS AND IN EXUDATES. M. G. COLVIN, *J. Infect. Dis.* **51**:527, 1932.

There is a nonspecific inhibitory effect of serum on bacteriophagy, which was first observed and reported by Gratia. This phenomenon associated with the lysis of staphylococci has been shown in connection with other organisms by subsequent investigators. In this report, the results of further investigations in regard to the importance of the various factors concerned in inhibition of bacteriophagy in body fluids are outlined. It has been found that variation of serum, body fluid, race of bacteriophage and bacterial strain or species introduces distinct differences in the amount of inhibition. Attempts to adapt a staphylococcic or a streptococcic phage to produce complete lysis in serum have been practically unsuccessful. It is shown that repeated contact with serum may have a tendency to make an organism lysis-resistant, and consequently an adaptation to resist lysis develops. A study of the mechanisms of inhibition to lysis shows that serum delays multiplication of the bacteriophage, but does not prevent specific fixation of the corpuscle. In the serum, the protein fraction is the main factor in inhibition of lysis, while in urine the crystalloid fraction inhibits. The observations suggest that bacteriophagy in the body is much modified as compared with test tube standards of lysis. This modification is in the direction of lessening the sterilizing capacity of the bacteriophage.

AUTHOR'S SUMMARY.

LÖWENSTEIN'S CULTURE METHOD FOR TUBERCLE BACILLI. W. HAYMAKER, W. EKHART and J. FREUND, *J. Infect. Dis.* **51**:562, 1932.

With Löwenstein's method, no growth of tubercle bacilli was obtained from thirty-eight samples of blood from tuberculous patients. In four cases of polyarthritis, three of rheumatic heart disease and one of chorea, no tubercle bacilli were found in the blood, either by the cultural method or by inoculation of guinea-pigs.

AUTHORS' SUMMARY.

BACTERIA CAUSING ACUTE CORYZA. L. HOYLE, *J. Path. & Bact.* **35**:817, 1932.

The results of extensive observation of the relation between appearances of *Bacillus influenzae* and pneumococci in the upper respiratory tract and the occurrence of attacks of acute coryza suggest that many of the more severe attacks of coryza may represent infections by these organisms.

AUTHOR'S SUMMARY.

THE FILTRATION OF HERPES VIRUS THROUGH GRADED COLLODION MEMBRANES.

W. J. ELFORD, J. R. PERDRAU and W. SMITH, *J. Path. & Bact.* **36**:49, 1933.

The size of the virus of herpes has been estimated to be from 0.1 to 0.15 microns by filtration experiments in which both cerebral and testicular strains of the virus were studied.

AUTHORS' SUMMARY.

PULMONARY TUBERCULOSIS WITH THE BOVINE TYPE OF THE BACILLUS IN THE SPUTUM. W. M. CUMMING, W. M. FOSTER and A. S. GRIFFITH, *J. Path. & Bact.* **36**:153, 1933.

The methods of the isolation and identification of tubercle bacilli of the bovine type from fourteen cases of pulmonary tuberculosis in England are described. The distribution of the cases is as follows: From 211 unselected cases of pulmonary tuberculosis in a northern urban industrial population (Bradford), six bovine strains were isolated. In five of these cases there had previously been a glandular lesion. Of fifty-one cases of pulmonary tuberculosis in the north of England (including the Bradford cases) in which there had been definite evidence of a previous glandular lesion, ten have been shown to be due to the bovine type of the bacillus. Of fourteen similar cases in the south, one has been shown to be due to the bovine type. Of fifty-nine cases of pulmonary tuberculosis in the north of England occurring in children under 16 years of age, one has been shown to be due to the bovine type. Of fifty-two similar cases in the south, two have been shown to be due to the bovine type. Of eleven cases of pulmonary tuberculosis occurring in patients coming much in contact with cattle, two have been shown to be due to the bovine type. In any given case of pulmonary tuberculosis, the presence of tubercle bacilli of the bovine type seems to be of definitely unfavorable prognostic significance. It is pointed out that the possibility of the occurrence of man-to-man and of man-to-cow infection with the bovine type of the tubercle bacillus becomes increasingly more difficult to ignore. At autopsy in two of the cases, it was established that the route of infection was alimentary and that the pulmonary lesion was indistinguishable from that due to the human type.

AUTHORS' SUMMARY.

TUBERCULOUS DISEASE IN CHILDREN: ITS PATHOLOGY AND BACTERIOLOGY.

JOHN W. S. BLACKLOCK, Special Report Series, No. 172, Medical Research Council, July, 1932.

In 1,800 autopsies on infants and children from a few hours old up to 13 years of age, Blacklock found gross evidence of tuberculosis in 283 (15.7 per cent). In 173 (61.1 per cent) of these the condition was considered due to primary infection of the lungs or of the thoracic lymphatics. The primary pulmonary lesion first described by Parrot, consisting of a localized patch of tuberculous bronchopneumonia which showed a tendency to heal, usually single and subpleural, was found in 148 of 173 cases in which the first site of infection was considered to be thoracic. These primary lesions were found most often in the right lung, the right upper lobe being most frequently involved. The apex of the upper lobe was seldom the seat of a lesion. The tracheobronchial glands in direct anatomic relation to these foci were always diseased. The lesions in the primary focus and related lymph glands were of the same age or that in the glands was more recent, so that a lymphogenous origin of the pulmonary focus seemed unlikely. No retrograde

spread from the tuberculous tracheobronchial glands back into the substance of the lung was observed. None of the primary foci could be shown to have a vascular origin; it is held that these primary pulmonary foci are aerogenic in origin. From the cases in which the primary lesion was found in the lung only the human type of bacilli were obtained, either from the lesion itself or from the regional glands. In 101 cases (35.7 per cent) of tuberculous lesions, the evidence was in favor of an abdominal site of the first infection. Of these, 18—all children under 5 years of age—showed intestinal ulceration, chiefly in the lower end of the ileum. All the children under 1 year of age with intestinal ulcers had been fed on cow's milk. In 83 cases, no ulcers were noted, but the mesenteric glands, chiefly in relation to the lower end of the ileum, were the seat of tuberculosis. The greatest number of primary abdominal lesions were found in the second year of life, that is, at a period when children were consuming large amounts of raw milk. Primary abdominal tuberculosis was less frequent than primary thoracic tuberculosis throughout all ages. There were fewer secondary lesions and less extensive glandular involvement in the cases with primary abdominal lesions than in these with primary thoracic lesions. From these abdominal lesions, 12 human and 54 bovine strains were isolated.

LUKE W. HUNT.

A CARBOHYDRATE COMMON TO THE GROUP OF ACID-FAST ORGANISMS, INCLUDING THE TUBERCLE BACILLI. ARNOLD BRANCH, *Tubercle* **13**:481, 1932.

Antiserums prepared in rabbits by the inoculation of whole bacterial vaccines of acid-fast organisms give a strong precipitin reaction with a carbohydrate isolated from filtrates of these organisms. This carbohydrate is common to a representative group of the acid-fast organisms, as determined by precipitin tests and passive anaphylaxis in guinea-pigs. The carbohydrate is not related to the pathogenicity or virulence of acid-fast bacilli, as it is present in the saprophytic *Mycobacterium phlei* and in avirulent strains of bovine (B C G) and avian (A1 [3]) tubercle bacilli. In order to produce specific antiserums for members of the acid-fast group of bacteria, it will be necessary to use antigenic fractions (protein or lipoid). The author used in these tests the human tubercle bacilli, H 37 and a strain from Cobbett; the bovine tubercle bacilli, B 1 (Saranac Lake), B 2 (Parker of Boston) and B C G; the avian tubercle bacilli, A 1 (Saranac Lake); two dissociates; two virulent strains (from Medlar and Schulz); three avirulent strains (porcine 81, Raw-Calmette and Raw Koch from Griffith); a timothy bacillus (from Lister Institute); *Mycobacterium thannopheus* (Aronson); *Mycobacterium marinum* (Aronson), and other acid-fast bacilli.

H. J. CORPER.

A LEPTOTHRIX PATHOGENIC FOR MAN (*LEPTOTHRIX PLEURITICA*). J. L. NICOD, *Ann. d'anat. path.* **9**:477, 1932.

A pulmonary lesion is described which was due to *Leptothrix pleuritica*. The lesion was a diffuse chronic granuloma. The organism resembles actinomyces, but differs in its staining reactions, its cultural characteristics and in the kind of granuloma that it produces, although the latter is not specific. It is believed that many atypical cases of actinomycosis are perhaps due to *Leptothrix pleuritica*.

PERRY J. MELNICK.

CONGENITAL TUBERCULOSIS BY ASPIRATION OF AMNIOTIC FLUID. GEORGES GANDU, *Ann. d'anat. path.* **9**:891, 1932.

The author discusses the portals of entry of the tubercle bacillus in congenital tuberculosis, and reports a case in which the infection resulted from aspiration of infected amniotic fluid in utero.

PERRY J. MELNICK.

THREE FIRST CASES OF RECURRENT FEVER OBSERVED IN TUNIS. C. NICOLLE, C. ANDERSON and J. LAIGRET, Arch. Inst. Pasteur de Tunis **21**:43, 1932.

The spirochetosis described as Spanish-African recurrent fever was recognized in Tunis. The organisms appeared to be carried by a tick, *Ornithodoros erraticus*, and to belong to the *Spirochaeta hispanica* (Buen) group, highly pathogenic for guinea-pigs. In common with other spirochetes of Tunis, the organisms seemed to be indifferent to the species of tick, in which the nymph and adult stages were infected, although the nymph stage was responsible for transfer. Lytic tests with the serum of infected animals indicated a marked specificity among the spirochetes of this group. Cross-immunity tests gave similar indications of specificity. "There are not, in the spirochetes of recurrent fever, species but individuals which one may arrange in groups, characterized by a common pathogenicity and by a common agent of natural transmission."

M. S. MARSHALL.

STATUS OF THE FIXED VIRUS OF RABIES. L. BALOZET, Arch. Inst. Pasteur de Tunis **21**:130, 1932.

The evolution of the fixed Pasteur virus in Tunis shows a more or less coincidental reduction in the period of incubation, an increase in neurotropic properties, and a considerable increase in sensitivity to physical and chemical agents. The Tunis strain has the shortest period of incubation so far as known of any descendants of the Pasteur virus, viz., five and three-fourths days. After three days' drying, it is no longer virulent. In the active state, however, it will infect by eye and often following subcutaneous injection. The evolution of the substrains of the original virus held in different institutes has not been identical.

M. S. MARSHALL.

TRANSITORY TUBERCULOUS BACTERIURIA WITH NEGATIVE TUBERCULIN SKIN TESTS. E. RAMEL, Arch. internat. de méd. expér. **7**:633, 1932.

A case is presented of an 8 year old child, healthy and clinically nontuberculous, who reacted negatively to the tuberculin skin tests but whose urine on two occasions was found to contain typical acid-fast bacilli, proved to be tubercle bacilli by inoculation in the guinea-pig. The syndrome is called transitory tuberculous bacteriuria. The authors present this case as one which is not explicable on the grounds of present theories of humoral antibodies.

RALPH FULLER.

MORPHOLOGIC STUDY OF THE VIRUS OF RABIES. M. C. LEVADITI, R. SCHOEN and M. J-G. MEZGER, Arch. internat. de méd. expér. **7**:655, 1932.

In mice, rats and monkeys inoculated with the street virus of rabies, it is possible to follow the changes in the germ of rabies within the neuron and to understand some of the intermediate phases in the development of the parasite, the protozoan character of which seems more and more probable.

RALPH FULLER.

POSTMORTEM OBSERVATIONS IN SYPHILITIC PATIENTS. G. GULDBERG, Arch. f. Dermat. u. Syph. **166**:730, 1932.

In patients with positive Wassermann tests, but without any other signs of syphilis, microscopic examination from four to fifteen years after the infection showed small specific cellular infiltrations in the aorta, in part with spirochetes, in the para-aortic tissue and in the fibrous tissue of the mediastinum. The inguinal, ilio-lumbar and mesenteric lymph nodes in these cases showed microscopically a chronic specific lymphadenitis, and in some of them spirochetes could be demon-

strated. These syphilitic foci with spirochetes may be the source of syphilitic processes in the vascular or nervous system, skin or viscera which develop many years after the infection.

AUTHOR'S SUMMARY.

ISOLATION OF TUBERCLE BACILLI FROM THE BLOOD IN TUBERCULOSIS OF THE BONES ACCORDING TO LÖWENSTEIN'S METHOD. A. URGOITI, Beitr. z. klin. d. Tuberk. **80**:480, 1932.

Sixty-seven patients with tuberculosis of the bones and thirty-nine controls were examined. No cultures were obtained from the controls. Twenty-six of the sixty-seven tuberculous patients yielded cultures. These studies were done in Löwenstein's laboratory.

MAX PINNER.

CULTIVATION OF THE TUBERCLE BACILLUS FROM THE BLOOD OF LÖWENSTEIN'S METHOD. H. J. TIEDEMANN, Beitr. z. Klin. d. Tuberk. **81**:450, 1932.

Blood cultures were made by Löwenstein's method in fifteen cases of acute polyarthritis. Although Löwenstein has reported positive results in almost 100 per cent of cases, in no case in this series was it possible to obtain growth of tubercle bacilli. Similar cultures made in fifteen instances of tuberculosis of the skin, ten of tuberculosis of the eye and four of schizophrenia were likewise consistently negative. In only two of fifty cases of far advanced, active, open pulmonary tuberculosis were tubercle bacilli demonstrable in the blood. In three other instances acid-fast rods were demonstrated either macroscopically or microscopically which were apparently not pathogens. That the method is essentially sound was demonstrated by the recovery of tubercle bacilli both from mixtures of normal blood and various amounts of bacilli in vitro and from the blood streams of animals experimentally infected, both subcutaneously and intravenously. The inconstancy with which the latter was achieved, however, suggests that invasion of the blood stream by the tubercle bacillus is not a frequent, nor as yet a fully elucidated, phenomenon.

AARON EDWIN MARGULIS.

BACTERIOLOGIC AND HISTOLOGIC RESEARCHES ON TUBERCLE BACILLEMIA. K. BROCK, Beitr. z. Klin. d. Tuberk. **81**:543, 1932.

The inconstancy and the rarity with which tubercle bacilli may be recovered by Löwenstein's method from the blood stream in cases of tuberculosis, and the lack of correlation with bacteriologic and histologic evidence of focalization in the spleen and the bone marrow, suggest that tubercle bacillemia is not regularly present in tuberculosis, and that when invasion of the blood does occur focalization in the bone marrow and spleen is not invariable.

AARON EDWIN MARGULIS.

MILIARY NECROSES IN THE NEW-BORN INFANT. W. IFF, Beitr. z. path. Anat. u. z. allg. Path. **86**:83, 1931.

Miliary necroses in the new-born infant occur in the liver, spleen, lungs and thyroid and are morphologically unlike any known granulomatous lesions.

Gram-positive short bacilli are occasionally found in these necrotic areas and may be the cause, since pure cultures injected into animals produce similar lesions. Entry is either placental or by vaginal aspiration.

W. S. BOIKAN.

ISOLATED ACTINOMYCOSIS OF THE KIDNEY. J. RAČIĆ, Beitr. z. path. Anat. u. z. allg. Path. **87**:474, 1931.

The author describes a case of long-standing renal pelvic stone, complicated by isolated actinomycotic pyelonephrosis. The patient recovered completely after opera-

tion. The author holds that actinomycosis can form a primary small encapsulated focus in the oral, gastro-intestinal (appendix) or respiratory tract from which an isolated active metastasis to a single organ—for instance, the kidney—can take place.

W. S. BOIKAN.

PATHOLOGIC-ANATOMIC DIAGNOSIS OF YELLOW FEVER IN MONKEYS. E. P. SNIJDERS and J. E. DINGER, *Virchows Arch. f. path. Anat.* **280**:444, 1931.

Seventy-six rhesus monkeys were given injections of yellow fever virus from various sources. This was done not without danger, for one of the authors (J. E. D.) contracted a mild case of the disease following a scratch from one of the monkeys. The course of the disease is short in these animals. Icterus and petechial hemorrhages were variable. Anatomically, the most characteristic lesions were in the liver. These included fatty degeneration and necrosis of the liver cells and the highly characteristic Torres intranuclear inclusion bodies. The latter are considered to be products of nuclear degeneration and have no relation to the virus. Their number has no relation to the virulence. The blood was found to be the most virulent in reproducing the disease. Noguchi's spirochetes could not be demonstrated in Levaditi stains.

PERRY J. MELNICK.

SOME UNUSUAL MANIFESTATIONS OF ECHINOCOCCUS DISEASE. H. SCHMIETA, *Virchows Arch. f. path. Anat.* **285**:650, 1932.

The author describes four somewhat unusual cases of human echinococcus disease. One was an alveolar echinococcus of the liver that had invaded the walls of the inferior vena cava and portal vein, causing great fibrous thickening of the walls of the vessels. One was a cystic echinococcus of the liver with marked deposition of hematoidin in the cyst. This phenomenon is rare in the cystic form of the disease, but is so common in the multilocular form as to be considered of diagnostic value in differentiating the two forms. The third case was one of primary cystic echinococcus of the spleen with multiple secondary cysts of the same organ, simulating grossly the alveolar form. The final case was one of cystic echinococcus of the mammary gland.

O. T. SCHULTZ.

MULTIPLE MULTILOCULAR ECHINOCOCCUS DISEASE. G. H. BARTSCH and A. POSSELT, *Virchows Arch. f. path. Anat.* **285**:665, 1932.

Multilocular echinococcus occurs most frequently in the liver, and multiple involvement is rare. In the case described by the authors, that of a man, aged 44, the disease of the liver had spread by direct continuity to the diaphragm, lower lobe of the right lung, right suprarenal, right kidney and local lymph nodes. There was metastatic involvement of the spleen, the upper lobe of the right lung and both cerebral hemispheres. The sequence of events could not be determined. Hooklets and heads were found only in the lesions of the brain.

O. T. SCHULTZ.

DOUBLE ANTHRAX INFECTION. L. GALVAN, *Virchows Arch. f. path. Anat.* **285**:686, 1932.

A 70 year old man who died of anthrax had a lesion of the dorsum of the hand and multiple small recent ulcers of the stomach that contained the bacilli. Both the cutaneous and the gastric lesions were believed to have been primary.

O. T. SCHULTZ.

PARALYTIC DEMENTIA AND SYPHILITIC AORTITIS. H.-J. SCHERER, Virchows Arch. f. path. Anat. **286**:183, 1932.

A number of recent writers have claimed that syphilitic aortitis is less frequent or runs a more benign course in persons with paralytic dementia than in those with nonparalytic syphilis. Scherer's investigation of this problem was based on the necropsy protocols and material of 202 cases of paralytica dementia. Syphilitic aortitis of varying grade was present in 125 of these. This group was compared with 125 cases of syphilitic aortitis in persons with nonparalytic syphilis. Scherer also studied 14 cases of juvenile paralysis and 19 of tables without paralysis. He could find no difference in the incidence of aortitis in the paralytic and in the nonparalytic groups. The subjective and objective clinical manifestations of aortitis were less frequent or less severe in the paralytic group. Aortitis and its sequels were a more frequent cause of death in the nonparalytic group; this was due to a lesser frequency of aortic insufficiency, aneurysm and other severe sequels of aortitis in the paralytic group. Cardiac hypertrophy was less evident in the paralytic group with aortitis; in the latter, the heart was more apt to be atrophic and flabby, as is the rule in paralysis. The most advanced forms of aortitis were anatomically no different in the two groups, but the localization of the process in the milder forms was atypical in the paralytic group. Analysis of the factors that might explain the differences that were found to exist brought to light the fact that the average age at death in the paralytic group was lower than that in the nonparalytic group, and that in the paralytic group without aortitis it was still lower. The severe forms of aortitis in the paralytic group not to be distinguished anatomically from the severe forms in nonparalytic syphilis, occurred in those persons who had reached an age equal to that in the nonparalytic group with advanced aortitis. No histologic differences in the aortitis of the two groups could be detected. The marasmus and enforced idleness of the persons with paralysis may be factors in the lesser degree of aortic and secondary cardiac involvement in this paralytic group. Whether marasmus exerts an influence through its effect on metabolism could not be determined. The author could find no reason to believe that the febrile therapy used in the treatment of paralytic dementia has any effect on syphilitic aortitis. In the 14 cases of juvenile paralysis there was one case of aortitis: the only conclusions drawn are that syphilitic aortitis does occur in juvenile paralysis, and that it is much less frequent than in the paralytic dementia of acquired syphilis. There is as yet not sufficient proof to substantiate the view, postulated by some, that there is a biologic antagonism between neurosyphilis and aortic syphilis.

O. T. SCHULTZ.

CULTIVATION OF TUBERCLE BACILLI FROM THE BLOOD STREAM. H. POPPER, F. BODART and W. SCHINDLER, Virchows Arch. f. path. Anat. **286**:615, 1932.

In a previous communication, the authors reported the results obtained by them with the Löwenstein method for the cultivation of tubercle bacilli as applied to blood obtained from the heart at necropsy. The present report presents the results of the use of this procedure in more than 1,000 examinations. The series includes the previously reported, and some additional, cultivations of blood obtained at necropsy. Positive cultures with macroscopic viable colonies were obtained in a high percentage of cases of miliary and other forms of active tuberculosis. Tissues obtained at biopsy and necropsy, exudates, urine and other similar materials also yielded a high percentage of positive cultures. In the postmortem examination of such materials and of the blood, the cultural method may replace animal inoculation. The negative results of the first 400 cultures of the blood stream were discarded because the Löwenstein technic had not been exactly followed. In the next 435 cultures of the blood during life, no macroscopic growth of tubercle bacilli was obtained. But microscopic examination revealed the presence of acid-fast and alcohol-fast rods in 11.5 per cent of the total. Microscopically positive results were obtained in 42.7 per cent of 7 cases of miliary tuberculosis and in

16.6 per cent of cases of advanced pulmonary tuberculosis. Löwenstein had claimed positive results in a relatively high percentage of cases of rheumatic fever and its complications or sequelae. In cases of this group, the present writers had 21 per cent of microscopically positive results in 38 cases of acute rheumatic fever, in 28.6 per cent of 7 cases of primary chronic polyarthritis, in 16.2 per cent of 6 cases of chorea minor and in 22.1 per cent of 9 cases of endocarditis of rheumatic origin. Five cases of multiple sclerosis, in cases of which Löwenstein had reported a high percentage of positive results, 4 of lymphogranulomatosis, in cases of which several investigators have recently again reported the presence of acid-fast bacilli, and 5 of mycosis fungoides yielded negative results. Positive results were obtained in 9.5 per cent of 21 cases of sepsis and in 6.8 per cent of 44 control cases. The acid-fast rods seen only microscopically in cultures of the circulating blood could not be made to grow when transplanted, except in one instance. This was a case of recurrent rheumatic endocarditis, in which the blood culture yielded a culturally and morphologically characteristic tubercle bacillus that produced typical lesions when inoculated into animals. Twelve strains of acid-fast and alcohol-fast bacilli that could be cultivated proved to be avirulent and culturally unlike the tubercle bacillus. The relatively high percentage of microscopically positive cultures of the blood stream in known cases of tuberculosis indicates that the procedure has value. But similar results in the rheumatic group of diseases indicates that such positive results must be interpreted with care until the relationship of acid-fast bacilli to these diseases is established.

O. T. SCHULTZ.

GENERAL ACTINOMYCOSIS. K. FELLINGER and G. SALZER, *Virchows Arch. f. path. Anat.* **286**:638, 1932.

The subject was a man, aged 59. The primary site of the disease was the lung. Invasion of the blood stream led to widespread generalization of the process, with meningitis and multiple actinomycotic lesions in the liver, spleen, kidneys, thyroid and thoracic vertebrae. The organism was cultivated at necropsy from the purulent lesions, the splenic pulp, and blood from the heart. The granulation tissue contained many giant cells.

O. T. SCHULTZ.

MYCOSIS FUNGOIDES IN A DOG. D. WIRTH and R. BAUMANN, *Virchows Arch. f. path. Anat.* **286**:651, 1932.

Multiple nodular lesions of the skin and internal organs consisted of pleomorphic granulation tissue identical with that of human mycosis fungoides. The tissue contained acid-fast bacilli similar to those described by Busny in mycosis fungoides.

O. T. SCHULTZ.

INFECTIOUS MYXOMATOSIS OF RABBITS. E. HAAGEN, *Zentralbl. f. Bakt. (Abt. 1)* **121**:1, 1931.

The virus of infectious myxomatosis of rabbits was carried in tissue culture through thirty passages with retention of its virulence. The virus in rabbits at the height of infection was present in the erythrocytes, leukocytes, serum, plasma, lungs, kidneys, lymph nodes, spleen, testes, liver and tears. The lungs, lymph nodes and spleen seemed to be the most infectious.

Cell changes, particularly nuclear inclusions, were found not only in the myxomatous tissue but also in the cornea and in the eyelids. These changes are not uniform; they differ in size, structure and staining and should not be identified with the virus, but should be considered merely as products of a reaction of the cells against the virus.

PAUL R. CANNON.

Immunology

STREPTOCOCCIC AGGLUTINATION IN CHRONIC ARTHRITIS AND ACUTE RHEUMATIC FEVER. B. J. CLAWSON, MACNIDER WETHERBY, E. H. HILBERT and H. E. HILLEBOE, *Am. J. M. Sc.* **184**:758, 1932.

Streptococcic agglutination titers were determined in patients with chronic arthritis and acute rheumatic fever for two strains of streptococci. The first strain was isolated from a patient with acute rheumatic fever and the second from a patient with chronic arthritis. The agglutination titers of patients with these conditions were compared with those of normal persons and of patients with scarlet fever and glomerulonephritis. With the rheumatic strain the agglutination titers in acute rheumatic conditions were higher than normal, while those in chronic arthritis were not. With the chronic arthritic strain the titers were higher than normal in both chronic arthritis and acute rheumatic fever, but higher in the latter. With both strains the titers were decidedly higher than normal in both scarlet fever and glomerulonephritis. In all tests, including those with normal serums, the chronic arthritic strain was agglutinated in higher dilutions than the acute rheumatic strain. The chronic arthritic strain appeared to be more sensitive to agglutination. These findings suggest that both chronic arthritis and acute rheumatic fever are streptococcic infections. The view that chronic arthritis is due to a specific strain is not supported, since the chronic arthritic strain was agglutinated in higher dilutions with serums of patients with acute rheumatic fever than with the serums of patients with chronic arthritis. The lack of strain specificity is also shown by the fact that both the rheumatic and the arthritic strains were agglutinated in higher dilutions with serums of patients with scarlet fever and glomerulonephritis than with the serums of patients with acute rheumatic fever and chronic arthritis.

AUTHORS' SUMMARY.

HISTOLOGICAL STUDIES OF HYPERSENSITIVE REACTIONS. L. DIENES and T. B. MALLORY, *Am. J. Path.* **8**:689, 1932.

The tuberculin type of hypersensitiveness represents the first stage of the immune response to parenterally introduced protein antigen. It occurs in uninfected as well as in tuberculous animals. A tuberculous infection quantitatively increases it, but does not alter it qualitatively. It may be demonstrable as early as the third day after sensitization.

AUTHORS' SUMMARY.

CHEMICAL COMPOSITION OF THE ACTIVE PRINCIPLE OF TUBERCULIN: XV. FLORENCE B. SEIBERT and BETTY MUNDAY, *Am. Rev. Tuberc.* **25**:724, 1932.

Since the constituent of tuberculin which is responsible for producing cutaneous reactions in tuberculous animals is contained in the tuberculin protein molecule, methods are proposed and described for obtaining this protein in chemically pure form. These methods are: (1) growth on a pure nonprotein synthetic medium, (2) ultrafiltration, effecting concentration and purification, and (3) a single precipitation with trichloroacetic acid. The chemical composition of the product TPT (tuberculin protein precipitated by trichloroacetic acid), including nitrogen and polysaccharide content, varies only within 1 per cent, and the potency based on the nitrogen content varies almost within the range of experimental error of the skin test. Solutions of TPT are relatively stable, and stock solutions of any strength, equal to or greater than that of old tuberculin, can be made. A solution one and six-tenths times as strong as old tuberculin has been made. An equally potent and pure product can be made by means of ammonium sulphate precipitation, but the process is more tedious and does not readily lend itself to quantitative chemical work. Standardization of tuberculin potency should be made by means of the intracutaneous skin test, a known standard being used as control for diagnostic

purposes. Koch's old tuberculin was analyzed by the same methods, and 707 mg. of protein was obtained from 100 cc. This was approximately as active per unit of nitrogen as TPT. When old tuberculin was made in the usual way, but from a synthetic medium, the yield of protein precipitated by trichloroacetic acid was 347 mg. per hundred cubic centimeters, exceeding the 295 mg. per liter obtained from a three month old culture of tuberculin on a synthetic medium and less than the 707 mg. per hundred cubic centimeters obtained from a sample of ordinary old tuberculin.

H. J. CORPER.

PROTECTION AGAINST TUBERCULOSIS WITH BCG IN GUINEA PIGS. KONRAD E. BIRKHAUG, *Am. Rev. Tuberc.* **27**:6, 1933.

The tuberculinogenic principle of BCG is similar to that possessed by virulent bovine and human tubercle bacilli. No appreciable difference obtains in tuberculous guinea-pigs between the allergic cutaneous reactions elicited with tuberculins produced by virulent tubercle bacilli and BCG, whether whole or dissociated into "R" and "S" variant colony cultures. The oral administration of BCG in newly born guinea-pigs fails to arouse regularly tuberculin sensitization or any increased resistance to virulent superinfection. The parenteral administration of BCG in guinea-pigs is capable of arousing localized tuberculous lesions which heal promptly without producing progressive tuberculous disease. The parenteral BCG vaccination of guinea-pigs regularly produces tuberculin sensitization and a significant tuberculo-immunity which is most marked in animals vaccinated intracutaneously and subcutaneously. Guinea-pigs parenterally vaccinated with BCG are relatively twice as refractory to progressive tuberculosis following virulent superinfection as the nonvaccinated animals. Cultivation experiments demonstrate that BCG may survive in the body of the guinea-pig as long as five hundred and seventy-seven days after inoculation without showing any tendency to produce progressive tuberculosis. Parenteral administration in guinea-pigs of large doses of the S smooth colony variant dissociated from BCG is capable of arousing localized tuberculous lesions which heal promptly without producing progressive tuberculosis. BCG cultivated under partial anaerobiosis in deep broth cultures fails to show any increased virulence for guinea-pigs, but rather loses its viability after several months' cultivation. The experimental data presented indicate that BCG is harmless as a vaccine and is capable of arousing an outstanding and significant tuberculo-immunity when administered to guinea-pigs by parenteral routes.

AUTHOR'S SUMMARY.

A RAPID METHOD OF PROTECTING THE PERITONEUM AGAINST PERITONITIS. B. STEINBERG, *Arch. Surg.* **24**:308, 1932.

Protection against peritonitis can be obtained by the intraperitoneal injection of killed colon bacilli. Protection is due to the responding hyperleukocytosis and phagocytosis.

N. ENZER.

SKIN-REACTING SUBSTANCES IN THE URINE IN ACUTE STREPTOCOCCAL INFECTIONS. E. T. CONYBEARE, *Bull. Johns Hopkins Hosp.* **52**:119, 1933.

Colloidal material extracted from the urine of patients suffering from acute infectious conditions associated with beta hemolytic streptococci is capable, in a high proportion of cases, of producing a delayed erythematous reaction when injected intradermally into susceptible subjects. Similar material extracted from the urine of clinically normal persons is, by comparison on the same test subjects, relatively inactive as to the property of producing a cutaneous reaction. Such material from the urine of patients with scarlet fever appears to contain the "erythrogenic toxin" (Okell) of the hemolytic streptococcus. The reaction-

producing factor present in the material extracted from the urine of patients with acute pharyngitis and erysipelas is not shown by the experiments described to be derived from the hemolytic streptococcus. The possible nature of this factor is discussed.

AUTHOR'S SUMMARY.

IMMUNITY TO HUMAN AND PASSAGE POLIOMYELITIS VIRUS. SIMON FLEXNER, J. A. M. A. 99:1244, 1932.

The passage of the virus of poliomyelitis through monkeys intensifies its infectivity for these animals and modifies its specific immunologic reactions. The changes undergone are quantitative and probably also qualitative. The modified virus preserves its immunizing power, in part at least, against recent strains of the human virus. Immune serums prepared with human and with monkey passage strains of virus exhibit quantitative differences in cross-neutralizing tests. Virus serum immunity can be produced in monkeys by the separate, simultaneous injection of one or more doses of virus and immune serum. The dangers of active poliomyelitic symptoms arising in the inoculated animals seem lessened by the combined treatment. The optimum manner of producing virus serum immunity has still to be determined. Monkeys that have proved wholly refractory to nasal instillations of the virus have been shown to be devoid of serum antiviral activity and to exhibit average susceptibility to the intracerebral inoculation of potent virus.

AUTHOR'S SUMMARY.

LOCAL SKIN REACTIVITY TO BACTERIAL FILTRATES. G. SHWARTZMAN, J. Exper. Med. 56:677 and 687, 1932.

Reactivating Effect of Blood Serum on Neutralized Toxic Filtrates: In this paper there are reported observations on a certain new reactivating property of normal and immune blood serums of various animal species. The effect of the reactivating serums consists in restoration of the toxicity in vivo and in vitro of completely neutralized meningococcus and *B. coli* reacting factors. The property is apparently nonspecific and heat-labile, lessens on storage and has no relationship to complement. Heating of immune serums to a temperature destructive for the reactivating property, but innocuous to the neutralizing antibodies, raises considerably their neutralizing potency. The possible immunologic significance of the reactivating property is discussed in this paper.

Formation of Reacting Factors in Vivo: A rabbit sensitized a week previously to some animal protein receives a preparatory injection of a potent bacterial filtrate into the skin. Twenty-four hours later the rabbit is given an intravenous injection of the same animal protein. In from four to five hours severe hemorrhagic necrosis appears at the site of the preparatory injection. The incidence of positive results is high. A single sensitizing injection and an incubation period of one week are sufficient. The test is highly specific unless repeated sensitizing injections of large doses of antigen are made. The necessary sensitization can be elicited with minute quantities of animal proteins. It is also possible to elicit severe reactions at the sites of the preparatory injections in nonsensitized rabbits on separate intravenous injections of nonbacterial antigens and homologous antibodies (i. e., passive transfer.)

AUTHOR'S SUMMARIES.

PREVENTION OF BARTONELLA ANEMIA IN RATS. D. PERLA and J. MARMORSTON-GOTTESMAN, J. Exper. Med. 56:777 and 783, 1932.

An aqueous lipid extract of ox spleen was prepared which protects adult male albino rats of carrier stock in a large percentage of instances against *Bartonella muris* anemia following splenectomy. It is suggested that the extract contains a specific hormonal substance.

Copper plays a rôle in the mechanism of resistance to *Bartonella muris* anemia in the rat. The small amount of the element in the ordinary diet of the rat is insufficient to protect the animal after splenectomy. An excess of copper, however, may give protection in the absence of the spleen. Its utilization would seem to be intimately associated with splenic function.

AUTHORS' SUMMARIES.

THE MATERNAL TRANSMISSION OF VACCINAL IMMUNITY IN SWINE. J. B. NELSON, J. Exper. Med. **56**:835, 1932.

The introduction of vaccinia virus into the skin of swine calls forth a typical vesicular reaction which may be followed by a solid immunity. This acquired state of resistance was utilized in determining the route of immunity transmission from sow to young. The suckling young of immune sows, vaccinated on the seventh day or earlier, showed no reaction to the virus. Their hand-fed litter mates, however, were susceptible and reacted with the formation of vesicles. These observations indicate that the porcine placenta is largely impermeable to protective substances, and establish the fact that colostrum functions as the vehicle for their transmission as it does for antibodies.

AUTHOR'S SUMMARY.

ADVANTAGE OF VIRULENT SMOOTH STRAINS OF TYPHOID BACILLI FOR VACCINES. F. B. GRINNELL, J. Exper. Med. **56**:907, 1932.

A study of the subcultures of the Rawlins strain of *Bacterium typhosum* used by twelve different laboratories for the production of vaccine showed that they all differed from recently isolated smooth strains in cultural characteristics, virulence and protective efficiency. Eleven of these Rawlins cultures gave both the flagellar and the somatic type of agglutination in antismooth rabbit serum, and the one culture so tested produced both flagellar and somatic agglutinins when injected into rabbits and man. Agglutination of neither the flagellar nor the somatic type can therefore be used as a test of the smoothness of a culture or as an index of immunity. Since the Rawlins strain differs from the smooth phase of *Bacterium typhosum* in cultural characteristics and in virulence and is much less efficient than smooth strains as a protective antigen, and since the selection and maintenance of smooth cultures suitable for vaccine production present no serious difficulty, it would seem but logical to substitute virulent, smooth cultures for the very old Rawlins strain, if one is to expect the maximum protection from antityphoid vaccination.

AUTHOR'S SUMMARY.

ACTIVE IMMUNIZATION OF MICE WITH THE POLYSACCHARIDES OF PNEUMOCOCCI, TYPES I, II AND III. J. ZOZAYA and J. CLARK, J. Exper. Med. **57**:21, 1933.

Pneumococcus polysaccharides, types I, II and III, adsorbed on collodion particles, and types I and III, adsorbed on carbon (nori), are antigenic in mice. Unadsorbed *pneumococcus polysaccharide* of type I is antigenic in mice in proper dilution. One preparation of type II polysaccharide is not antigenic, while another one immunized against types I and II. Type III polysaccharide is only slightly antigenic against type III, but immunized against type I. The antigenicity of *pneumococcus polysaccharide* in optimal dosage is tentatively explained by an adsorption phenomenon taking place in the body in instances in which the polysaccharide has not been adsorbed before injection. The aggressin-like action of large doses of *pneumococcus polysaccharides*, types I, II and III, is further established.

AUTHORS' SUMMARY.

IMMUNOLOGICAL REACTIONS BETWEEN AGAR-AGAR AND SOME BACTERIAL ANTISERA. J. ZOZAYA and L. MEDINA, J. Exper. Med. **57**:41, 1933.

As found by Sordelli and Mayer, agar adsorbed on bacteria produces agar-reacting antibodies in animals receiving injections of these organisms. False cross-

agglutination and precipitin reactions can be produced in serums containing agar-reacting antibodies by organisms grown on agar. Zozaya's publication in this field requires partial revision on this account. There is suggestive immunologic evidence of chemical similarity between the specifically reactive groups of agar-agar, and the C substance of the pneumococcus.

AUTHORS' SUMMARY.

HUMAN IMMUNITY REACTIONS TO PNEUMOCOCCI OTHER THAN TYPES I, II AND III. M. FINLAND and W. D. SUTLIFF, J. Exper. Med. 57:95, 1933.

A group of seventy-two human subjects were studied with respect to the immune reactions of their blood and serums to pneumococci, types I, II and III, and to four other types (V, VI, VIII and IX) previously included in group IV. The same general relationships were observed for all of these types as were previously demonstrated for types I, II and III. Each type was specific in relation to the bactericidal action of normal human blood and the protective action of normal human serum. The frequency with which pneumococcal action for any pair of types was present for both or absent for both in the same samples of blood was slightly greater than that calculated from the frequencies with which each of the types was killed separately. No closer correlation could be demonstrated between the reaction of the blood of these subjects to types II and V and the reaction to types III and VIII (types related in their reaction to artificially prepared immune serums) than was observed between unrelated strains.

AUTHORS' SUMMARY.

ALLERGIC LOBAR PNEUMONIA. B. M. FRIED, J. Exper. Med. 57:111, 1933.

The injection of small amounts (1 cc.) of horse serum into the lungs of normal rabbits produces a transient pneumonitis confined to the dorsal aspect of both lungs. The injection of the same amount of horse serum into the lungs of rabbits that have been previously sensitized to the same serum causes, in a high percentage of cases, a lesion which is confined to one lung, with the gross and microscopic features of lobar (fibrinous) pneumonia in man.

AUTHOR'S SUMMARY.

NATURAL AND ACQUIRED RESISTANCE IN PROTOZOA TO THE ACTION OF ANTIGENIC POISONS. C. H. PHILPOTT, J. Exper. Zool. 63:553, 1932.

Venoms have been found to be very satisfactory as representative antigenic poisons for use in the study of natural and acquired resistance in protozoa to agents that produce immunity in higher animals. Paramecia belonging to the same clone, but grown in different environments, show less difference in resistance to venoms than animals of different clones grown in similar environments. Thus it seems that genetic factors are more important under ordinary conditions than environmental factors in determining resistance in Paramecia. The resistance to venom in a clone of Paramecia gradually decreases when the animals are grown for long periods of time in uniform culture mediums. The resistance to venom in a clone of Paramecia fluctuates from time to time, even when the animals are grown under uniform conditions. This fluctuation in resistance is general rather than specific; i. e., at the time that the resistance increases or decreases for one venom, it changes correspondingly for another. When Paramecia are exposed at intervals through long periods of time to the action of a venom, hypersensitiveness to the poison first develops. As treatments are continued the animals gradually recover from this and display a certain amount of resistance. This resistance is never great, and in this respect resembles the tolerance which animals acquire to ordinary poisons rather than immunity to antigens. The acquired resistance is specific in the sense that resistance to a venom does not protect the animals from an unrelated venom. The acquired resistance is also temporary and is soon lost when the animals are no longer treated.

AUTHOR'S SUMMARY.

STUDIES IN ANAPHYLAXIS IN THE RABBIT. ELLA F. GROVE, *J. Immunol.* **23**:2, 101, 1932.

The technic employed by Grove brought about maximal sensitiveness to egg white and horse serum in 70 per cent of rabbits, while about 25 per cent remained insensitive. Different modifications of the technic gave inferior results. A subcutaneous injection one week after the peak of sensitiveness was reached led to a diminution of sensitiveness, but did not influence the titer of the antibodies. There was no direct connection between the degree of precipitin production and sensitization though in the rabbits treated with egg white the passively sensitizing property of their serum was, in general, parallel to the precipitin titer. The development of the Arthus phenomenon was no criterion of the degree of sensitization. It was present without a high degree of sensitization, and vice versa. The lack of response to sensitization in about 25 per cent of rabbits was not due to hyposensitivity of their shock tissues, as evidenced by the observation that they died with anaphylactoid symptoms following injections of barium chloride, which, in smaller doses, acts primarily on the shock tissues affected in the general anaphylactic reaction. There were differences in the response of unstripped muscles from various parts of the body of rabbits and guinea-pigs to the addition of histamine, epinephrine and barium chloride to the Dale bath. The same substances produced different responses in the different muscles, and the same muscles reacted differently to the different substances. The effect of these substances in the living animal was not always reflected in the action on the isolated muscle. Rabbits became uniformly and maximally sensitized with fowl corpuscles. Aqueous extracts of fowl corpuscles had only slight antigenic qualities *in vitro* and none *in vivo*. Rabbits treated with goose corpuscles yielded immune serums toxic for guinea-pigs. The ability of guinea-pig kidney to absorb the toxic substance throws some doubt on the view that goose corpuscles are free from Forssman's antigen. The Arthus phenomenon was observed in almost all rabbits sensitized with fowl corpuscles. Spiral strips of the pulmonary artery of sensitized rabbits contracted in the Dale bath after addition of the specific antigen, while the bronchial strip did not show this response. The response of the bronchial strip to histamine was slight. The weakness of the unstripped musculature of the bronchus explains that phenomenon. The experiment corroborates the view of Simonds concerning the symptomatology of acute anaphylactic shock in rabbits. The absence of contraction of the urinary bladder in rabbits was to Manwaring an evidence of lack of participation of unstripped muscle in acute anaphylactic shock in that animal. Grove showed that in the guinea-pig contractions of the urinary bladder are due to asphyxia. This condition is absent in the rabbit, and therefore contraction of the bladder does not occur. When asphyxia is produced experimentally, contractions of the bladder also result.

I. DAVIDSOHN.

AGGLUTINATION REACTIONS IN RHEUMATOID ARTHRITIS. MARTIN H. DAWSON, MIRIAM OLMSTEAD and RALPH H. BOOTS, *J. Immunol.* **23**:187, 1932.

Serums of patients with rheumatoid arthritis agglutinated in high dilutions strains of hemolytic streptococci, coming from different sources, equally as well as the so-called typical strains of Cecil, Nicholls and Stainsby. Of various other gram-positive cocci, only R strains of pneumococci were agglutinated in high dilutions. Serums of patients suffering from different diseases possessed only very low agglutinating properties for the hemolytic streptococci. Serums of normal controls did not agglutinate at all. The agglutinating titer rises with the duration of the disease and with the age of the patient. Absorption experiments showed lack of specificity among the various agglutinated strains of hemolytic streptococci. The R pneumococci absorbed the agglutinins from the patients' serums but not as fully as the streptococci. The agglutinins show the same thermal properties as normal antibodies. In no case could streptococci be isolated from the blood of patients suffering from rheumatoid arthritis. Dawson and his associates

emphasize that there is no compelling evidence of a relationship between the presence of agglutinins in the blood and the etiologic rôle of hemolytic streptococci in the production of the disease.

I. DAVIDSOHN.

TUBERCULIN TESTS IN INFANTS VACCINATED WITH BCG. R. DEBRÉ, M. LELONG and PICTET, *Ann. Inst. Pasteur* **49:4**, 1932.

Careful tuberculin tests were performed periodically on 297 infants vaccinated by mouth with BCG and on 193 unvaccinated infants. Both groups were under adequate control, and were protected from contact with tuberculosis. The large control group, members of which consistently presented negative reactions, is offered as a measure of the rigorous control in the technic used. In the vaccinated group 97 per cent showed positive reactions at 2 years, the maximum. At 3 months, 73 per cent showed reactions; at 6 months, 89 per cent, and at 1 year, 91 per cent. The degree of sensitivity increased with age also, during this period, and thereafter remained constant at least up to 5 years, the age limit of the group tested.

AUTHORS' CONCLUSIONS.

CUTANEOUS PASSIVE IMMUNIZATION AGAINST TETANUS. A. URBAIN, *Ann. Inst. Pasteur* **49:103**, 1932.

Favorable results were secured in the prevention and cure of tetanus intoxication or infection in guinea-pigs. Tetanus antitoxin, of a potency of 3,000 units (international) per ten cubic centimeters, was mixed with a petrolatum and hydrous wool fat base. The ointment, in lethal doses, was applied to the shaven and slightly scarified skin of test animals between twenty-four hours preceding the injection either of toxin or of spores mixed with staphylococci and three hours after such injections. This afforded a fair degree of protection; the action was specific.

M. S. MARSHALL.

SANARELLI AND SHWARTZMAN REACTIONS. A. GRATIA and R. LINZ, *Ann. Inst. Pasteur* **49:131**, 1932.

The Sanarelli reaction (1924) was based on the observation of rapid death in an animal given an intravenous injection of a tolerated dose of cholera organisms and, the next day, a filtrate of an otherwise harmless organism, like *Proteus*, by the same route. The Shwartzman reaction (1928) is based on the local skin reaction at the site of injection of an innocuous filtrate when a similar filtrate is given intravenously the next day. In an exhaustive study the authors conclude that the phenomena are identical, and they reveal many positive and negative factors too numerous to abstract properly. Young rabbits and guinea-pigs gave reactions; rats and mice did not. Observation of the skin of rabbit ears had certain advantages, but the intestines, kidneys and lungs also showed hemorrhagic reactions. At least five or six hours were necessary between injections. In a strong reaction circulatory changes similar to those observed in anaphylaxis occurred. Intravenous injections of a filtrate of *Bacterium coli* produced hemorrhagic reactions in animals prepared with a number of visible and invisible viruses. It is believed that a number of clinically observed hemorrhagic conditions are based on similar phenomena.

M. S. MARSHALL.

VASCULAR REACTIONS IN ISOLATED ORGANS. V. ZERNOFF, *Ann. Inst. Pasteur* **49:358**, 1932.

"The method of isolated vessels permits the study of vascular reactions in a simple and precise manner. Bacterial cultures (*Danysz' bacillus*, heated *Vibrio cholerae*) have no pronounced action. . . . Tuberculin provokes vascular contraction. Toxins of diphtheria, tetanus and *Clostridium edematiens* produced a

strong contraction. The method permits the study of anaphylactic shock in vitro. The passage of antigen induces a violent contraction of isolated peripheral vessels of sensitized animals. . . . Horse serum produces no reaction in the isolated vessels of nonsensitized animals. The sensitivity of isolated vessels may be controlled by epinephrine. They react to dilutions of 1:10,000,000. After isolation of a rabbit's ear the life of the vessels may be preserved for several days (eighteen days and longer). The death of the organism does not signify the death of the tissues."

M. S. MARSHALL.

VACCINATION AGAINST TYPHUS. CHARLES NICOLLE and HÉLÈNE SPARROW, Arch. Inst. Pasteur de Tunis **21**:25, 1932.

The method of Weigl, consisting of vaccination by means of a phenolized suspension of the intestines of infected lice, was tested. Although Old World typhus is less dangerous to laboratory workers than American strains, the Weigl vaccine is being used, since all experimental tests were favorable.

M. S. MARSHALL.

SKIN REACTIONS TO VARIOLA, VACCINIA AND VARICELLA. PAUL DURAND and ERNEST CONSEIL, Arch. Inst. Pasteur de Tunis **21**:73, 1932.

Variola or vaccinia left a state of skin reactivity to either virus. This was not true of varicella; there was no reaction with varicella virus or with the heterologous viruses. The reaction is considered an immunity reaction, distinct from the sensitivity group (tuberculin and others) and the "reactivity" group (diphtheria toxin, etc.). Varicella is thus considered as distinctly separate from related vaccinia and variola, and a means of checking relationships between animal pox diseases is afforded. The technic used consisted of intradermal inoculations of specially prepared antigen, following which local reactions were relatively rapid (in four or more hours). The phenomenon is thus not the usual immunity reaction to vaccine virus, the disadvantages of which are pointed out by the authors.

M. S. MARSHALL.

ANAPHYLACTIC SHOCK IN TISSUE CULTURES. ENRICO SERENI and LIVIA GAROFOLINI, Arch. f. exper. Zellforsch. **13**:53, 1932.

If cells of the spleen, bone marrow or epiploon of a chicken sensitized against horse serum are cultured in a medium to which small amounts of the antigen are added (from 1:10,000 to 1:20,000), an anaphylactic shock occurs, manifesting itself by extensive cellular degeneration. The hypersensitivity is, however, preserved only up to the third passage in a normal medium. Cells can also be sensitized in vitro by adding small amounts of the antigen to the medium. The sensitization develops quickly and disappears after six or seven days (three passages). An active sensitization against the antigen in vitro cannot be obtained if cells of other organs (heart, kidney, liver, stomach, testis) are used. It occurs, however, if these tissues are explanted in a sensitized serum. A passive sensitization of these tissues is therefore possible. An active sensitization is obtained when liver and spleen present in the culture medium, as the splenic tissue apparently excretes antibodies into the medium. The anaphylactic antibody formation is exclusively bound to the hematopoietic organs.

WILHELM C. HUEPER.

THE TEMPORAL FACTOR IN THE APPEARANCE OF IMMUNITY IN EXPERIMENTAL TUBERCULOSIS. E. BRUDNICKI, Beitr. z. Klin. d. Tuberk. **81**:579, 1932.

Endeavoring to determine the time relationship between primary tuberculous infection and the appearance of detectable immunity, guinea-pigs were reinfected at

progressively greater intervals. It was found that the shortest interval between infection and reinfection in which altered reaction to the latter could be demonstrated was four days. The differentiation became more striking as the time interval was increased.

AARON, EDWIN MARGULIS.

SUSCEPTIBILITY TO SCARLET FEVER AND BLOOD GROUPS. H. NAVAK, *Monatschr. f. Kinderh.* **54**:343, 1932.

Evidence is presented in favor of a greater susceptibility to scarlet fever in children of group O than in children of group A.

MORPHOLOGIC BLOOD PICTURE IN HUNGER AND IN ENTERAL SENSITIZATION AND ANAPHYLAXIS. W. N. NEKLUDOW and E. A. NEKLUDOWA, *Virchows Arch. f. path. Anat.* **280**:374, 1931.

Several series of guinea-pigs were sensitized to egg albumin by the enteric route. Reintroduction of the same antigen into the stomach from two to three weeks later resulted in anaphylactic shock. Hunger intensified these reactions by making the mucous membrane of the gastro-intestinal tract more permeable to the foreign protein. Eosinophilia was noted during the period of sensitization and during shock, but was even higher after oft-repeated enteric introduction of the foreign protein. During shock there is an increase of the pseudo-eosinophils and a fall in lymphocytes.

PERRY J. MELNICK.

ALLERGIC TISSUE REACTION DUE TO HOMOLOGOUS BLOOD. H. GEISSENDÖRFER, *Virchows Arch. f. path. Anat.* **285**:385, 1932.

To determine whether the local allergic tissue reaction that follows the introduction of a foreign antigen is due to the fact that the antigen is foreign to the species, the author injected whole guinea-pig blood into guinea-pigs. In one series each animal received its own blood, and in another series blood from other animals of the same species. The injections were made subcutaneously or intraperitoneally. The first injection consisted of 1 cc. of blood; the second, of 0.5 cc. introduced twenty-one days after the first. The first injection of the animal's own blood caused no local reaction. The first injection of the blood of another animal of the same species caused a slight lymphocytic and monocytic reaction. The second injection induced a local reaction identical qualitatively with that following the injection of heterologous blood, but somewhat less marked in degree.

O. T. SCHULTZ.

Tumors

ANALYSIS OF ONE HUNDRED AND FOUR CASES OF CARCINOMA OF THE LARGE INTESTINE. H. T. KARSNER and B. CLARK, JR., *Am. J. Cancer* **16**:933, 1932.

Carcinoma of the large intestine may assume projecting or polypoid, infiltrating and ulcerative and stenosing forms. Excess production of mucus may occur in any of the forms, but most often observed in the infiltrating, well differentiated adenocarcinomas. The term mucinous carcinoma is literally more correct than colloid carcinoma. The character of the tumor is determined by its cellular content and arrangement rather than by its incidental production of mucin. Extension and metastasis of rectal cancers are somewhat more frequent than of cancers of the colon, probably owing to differences in lymphatic drainage. Widespread metastasis is infrequent. Lymph nodes may be notably hyperplastic and not the seat of metastasis. Adenomatous polyps frequently become malignant. It is not established that all cancers of the large intestine originate in adenomatous polyps, but it may well be that this is true of about 40 per cent. The presence of marginal

adenomatous polyps may be an irritation phenomenon and not a proof of the origin of the cancer from polyps. Grading on the basis of microscopic criteria makes it probable, as regards rectal cancers, that as anaplasia increases, the age incidence, duration of symptoms and length of life decrease. In the series of cancers of the colon reported here, the higher degrees of anaplasia in cancers of the cecum and ascending colon affect the figures for the entire colon, so that the grades are definitely of higher order in the colon than in the rectum. This has yet to be established satisfactorily on the basis of a sufficient number of observations. It may serve as a basis of comparison of malignancy in tumors of the colon, but does not indicate practically that they are more malignant than rectal cancers.

FROM AUTHORS' SUMMARY.

PRIMARY TUMORS OF THE OS CALCIS. B. L. COLEY and G. S. SHARP, *Am. J. Cancer* **16**:1053, 1932.

The os calcis is an infrequent site of a primary bone tumor; but thirty-two cases were found in a combined study of the records of the Bone Tumor Department of Memorial Hospital and of the Bone Sarcoma Registry of the American College of Surgeons. Indefiniteness of clinical manifestations and of roentgenographic findings makes a positive preoperative diagnosis extremely difficult. An accurate diagnosis is essential for correct treatment. It follows that this can be obtained in most cases only by histologic study. If aspiration biopsy is inconclusive, as it often is, a surgical biopsy is indicated. In osteogenic sarcoma the treatment is early amputation. We do not favor prolonged irradiation preliminary to amputation, but, if adequate radiation can be delivered in a brief period, followed promptly by amputation, we see little objection to its employment; we have no data to suggest that the results are thereby improved. Endothelial myeloma, being an extremely radiosensitive tumor and characterized by early and wide dissemination to other bones as well as the lungs, is best handled by irradiation with high voltage x-rays and injections of mixed toxins of erysipelas and *Bacillus prodigiosus*. A giant cell tumor may be treated successfully by irradiation alone. There are, however, a number of cases of tumors in other bones in which irradiation has been used in the past in doses that have caused permanent damage to the skin, soft parts and bone. The response to irradiation varies considerably in individual cases of giant cell tumors. Thorough curettage, followed by an escharotic, such as zinc chloride or phenol and alcohol, is an established method of dealing successfully with these cases, particularly when the tumors are well defined and have not broken through the cortex and extended into the soft parts. The combined case records of the Memorial Hospital and the Bone Registry show that an early, correct diagnosis was seldom achieved, and that there was no well conceived plan of treatment for primary tumors of the os calcis.

AUTHORS' SUMMARY.

XANTHOMA OF THE BREAST. C. D. HAAGENSEN, *Am. J. Cancer* **16**:1077, 1932.

Xanthomas in general have been discussed, and tumors of the breast containing xanthoma cells have been classified as follows: primary xanthoma, a very rare tumor composed wholly of xanthoma cells and arising as a local manifestation of the syndrome of xanthomatosis; secondary xanthomatous degeneration, frequently encountered in true neoplasms, inflammatory processes and traumatic fat necrosis. Three cases of primary xanthoma of the breast and illustrative cases of secondary xanthomatous degeneration occurring in fibro-adenoma, in chronic abscess of the breast and in traumatic fat necrosis in the breast have been described.

AUTHOR'S SUMMARY.

LIPOMA. F. E. ADAIR, G. T. PACK and J. H. FARRIOR, *Am. J. Cancer* **16**:1104, 1932.

The salient clinical features of 352 lipomas occurring in 134 patients are reported. A clinicopathologic classification of lipomas is given, with illustrative case reports. Evidence is submitted in support of the theory that multiple lipomas are neurogenic tumors.

AUTHORS' SUMMARY.

GENETIC STUDIES ON THE TRANSPLANTATION OF TUMORS. J. J. BITTNER, *Am. J. Cancer* **16**:1144, 1932.

Rhythms of growth do not occur in the transplanted tumor cell. The theories of adaptation and virulence are no longer necessary. Intrinsic genetic factors determine the physiologic characteristics of both the host and the tumor cell.

AUTHOR'S SUMMARY.

THE MALIGNANT CELLS OF WALKER RAT SARCOMA No. 338. M. R. LEWIS and W. H. LEWIS, *Am. J. Cancer* **16**:1153, 1932.

The malignant cells of the Walker rat sarcoma 338 differ from normal fibroblasts. They are larger, the cytoplasm is denser and more granular, and the mitochondria are smaller and more numerous. Their nucleus is large and granular and shows no nucleoli. There is a pronounced central area. There are more cells with two or more nuclei than are found in cultures of normal fibroblasts. The number of atypical, abortive and abnormal mitoses is far greater than in cultures of normal cells, and there is apparently great variation in the number of chromosomes. Aberrant chromosomes are common. They form chromosome vesicles. The duration of mitosis, especially the metaphase, is prolonged. It has been suggested that malignancy may be bound up with permanent alteration of the centrosomal apparatus rather than with abnormal chromosome complexes, and that the latter are the result of the former.

AUTHORS' SUMMARY.

SOLITARY MYELOMA (PLASMACYTOMA) OF THE FEMUR. W. G. HARDING, JR. and T. S. KIMBALL, *Am. J. Cancer* **16**:1184, 1932.

A case of solitary plasma cell myeloma of the femur is reported. The nine cases of solitary myeloma recorded in the literature are reviewed. Complete roentgenographic and postmortem examinations were made in the case reported.

AUTHORS' SUMMARY.

IS THE INCREASE OF CANCER REAL OR APPARENT? M. T. MACKLIN, *Am. J. Cancer* **16**:1193, 1932.

Cancer is increasing, and it is increasing particularly in the age group over 60. It is not occurring at progressively younger ages or attacking larger percentages of the younger population. Despite the increase in cancer, deaths are fewer from all causes now than they were. More ground has been won from the ravages of infectious disease than has been lost to those disorders which are dependent on qualities inherent in the chemical and physical make-up of the patients. Cancer is increasing because, by preventive methods, there has been created a larger population to grow old, and, having grown old, they are kept from dying of those ills from which they formerly suffered. With each increase in the warfare against preventable diseases, there will be an increase in the ravages of cancer, for with each victory there is created a greater population to die from that disease. These conclusions are based on the statistics of Canada. There is strong ground for believing that a similar analysis of the statistics of any other country would lead to the same conclusions. It is true that there may be racial differences in immunity

to cancer, but the conclusion here reached will probably prove universal, namely, that excellent measures for the public health and high cancer rates are inseparable, at least for the present. Those who point to the low cancer rates existing among primitive peoples and who state that cancer is a disease of modern civilization neglect to call attention to the fact that preventive medicine is itself a triumph of modern civilization.

AUTHOR'S SUMMARY.

"FIBROMYOSIS": AN UNCLASSIFIED PLEXIFORM ENDOLYMPHATIC PROLIFERATION OF THE UTERUS. R. T. FRANK, *Am. J. Cancer* **16**:1326, 1932.

Based on the study of three cases of strikingly similar nature, the following conclusions seem warranted. Diffuse endolymphatic fibromyositis of the uterus, although rare, appears to form a distinct entity. The onset is characterized by marked and repeated uterine hemorrhages. A slow, uniform and symmetrical enlargement of the uterus occurs. From the findings a clinical diagnosis of myoma or adenomyoma is warranted. At operation the findings are such as to justify a similar diagnosis, and consequently supravaginal hysterectomy is performed. From the gross specimen, the pathologist makes the diagnosis of diffuse adenomyositis or functional "fibrosis." Microscopic study shows diffuse endolymphatic distribution with no evidence of a primary site. The endometrium is normal. From the cases so far observed, this type of neoplasm appears to be slow-growing and with only a moderate degree of clinical malignancy. No final conclusion as to its radio-sensitivity can as yet be offered.

AUTHOR'S SUMMARY.

XERODERMA PIGMENTOSUM. M. M. COPELAND and H. E. MARTIN, *Am. J. Cancer* **16**:1337, 1932.

Four cases of xeroderma pigmentosum are reported. The disease begins early in life, usually before the second year. The manifestations of the disease are reddening and pigmentation (lentigines) followed by roughening, dryness and ulceration of the skin. These changes are often associated with the formation of telangiectases and tumor-like processes, including basal cell and squamous cell carcinoma. The clinical course is characterized by progressive changes with moderate remissions, invariably running a prolonged but fatal course. The principal exciting cause seems to be exposure to the actinic rays of the sun in patients predisposed to the disease. The occurrence of the predisposition has been ascribed to a congenital susceptibility. While the skin has been considered the site of the predisposition, it is not clear what rôle is played by chemical disturbances in the blood and peripheral tissues. A trophoneuritic or nervous origin has been suggested, but there is lack of proof, and this is no longer considered feasible. Hematoporphyrin (a photodynamic substance) has been recently cited as a possible factor in bringing about the disease. The data at hand do not support the contention that a photodynamic substance is a causative factor in xeroderma pigmentosum. Disturbances in the glands of internal secretion are not as yet correlated with the disease process. Treatment has been divided into two major groups: treatment directed toward checking the progress of the disease and that directed toward curing certain local manifestations, such as ulcerations and neoplastic processes.

AUTHORS' SUMMARY.

BENIGN TUMORS OF THE BRONCHUS. P. GEIPEL, *Frankfurt. Ztschr. f. Path.* **42**: 516, 1932.

The author describes a case of basal cell carcinoma of the bronchus and a case of adenomatous polyp of the bronchus. The literature of benign bronchial tumors is reviewed.

O. SAPHIR.

MULTIPLE MYELOMA WITH DIABETES INSIPIDUS. H. G. ARONSOHN, *Virchows Arch. f. path. Anat.* **281**:78, 1931.

Aronsohn reports a case of multiple myeloma in which diabetes insipidus developed in the final few weeks before death; he states that this symptom in multiple myeloma has been reported only twice previously. At necropsy, it was found that a tumor mass growing in the sphenoid had produced localized defects in the floor of the sella turcica and in the body of the sphenoid. Aronsohn ascribes the diabetes insipidus to the action of the tumor on the hypophysis, but leaves undecided whether it acted directly on the gland or only interfered with the blood supply of the gland.

O. T. SCHULTZ.

CARCINOMA OF THE PROSTATIC URETHRA WITH IMPLANTATION METASTASIS IN THE ANTERIOR URETHRA. W. GEISLER, *Virchows Arch. f. path. Anat.* **281**:88, 1931.

A man, aged 64, who died of urosepsis following urinary retention, was found at necropsy to have a primary papillary carcinoma of the prostatic urethra. The tumor was very cellular and anaplastic. The fossa navicularis was occupied by an implantation metastasis of similar character that was not visible at the external urethral orifice. In the literature, primary carcinoma of the urethra is more frequent in women than in men.

O. T. SCHULTZ.

LOCAL ALLERGY AND HYPERKERATOSIS. O. REUTERWALL, *Virchows Arch. f. path. Anat.* **281**:483, 1931.

This experimental investigation had its inception in the thought that cancer may be a local allergic manifestation. Egg white was injected subcutaneously into the ears of rabbits. The injections were usually repeated twice a week over long periods of time and were always made into the same area. Reinjection led to an acute local anaphylactic reaction. In some of the animals this reaction was followed by hyperkeratosis of the ear. Only one such lesion regressed spontaneously. Animals with persisting hyperkeratotic lesions had not been under observation long enough to determine whether the epithelial proliferation would assume the characteristics of malignancy.

O. T. SCHULTZ.

CARCINOMATOUS MURAL THROMBOSIS OF THE HEART. R. WINTER, *Virchows Arch. f. path. Anat.* **282**:99, 1931.

In a case of carcinoma of the pancreas, the tumor spread by way of the portal vein and the inferior vena cava. Multiple thrombi were present on the endocardium of the right side of the heart, on the tricuspid valve and on the chordae tendineae of the tricuspid. The more recent thrombi contained tumor cells. Carcinoma cells were not present or were in a state of degeneration in organized thrombi. Winter believes that emboli of tumor cells became attached to the endocardium, which they destroyed by their proteolytic activity. A thrombus formed at the point of denudation, the carcinoma cells being enmeshed in the thrombus. As the thrombus organized, the tumor cells degenerated and eventually disappeared. A similar process was observed in the larger branches of the pulmonary artery. Tumor emboli that completely occluded terminal arterioles and capillaries did not lead to thrombosis and were able to grow through the walls of the vessels and to establish themselves as metastases.

O. T. SCHULTZ.

Medicolegal Pathology

PENETRATION OF FLUIDS INTO THE RESPIRATORY AND DIGESTIVE SYSTEMS FOLLOWING SUBMERSION OF DEAD BODIES. B. MUELLER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **19**:488, 1932.

Experiments on eighteen corpses of adults showed that a few minutes after submersion fluids had entered the trachea down to the middle-sized bronchi, the

esophagus and, in a few cases, the stomach; fluids were never found in the duodenum or in the peripheral areas of the lungs. Submersion of twenty-two dead bodies of new-born infants disclosed that fluids would penetrate the upper respiratory tubes, the esophagus and the stomach if the infants had been born alive and had breathed. The same findings were encountered in stillborn babies if artificial respiration had been applied prior to submersion, because of air being forced in to inflate the lungs and stomach. Escape of gas present in the stomach or in the air passages while the dead body was submerged allowed the fluids to penetrate the lungs and stomach rapidly.

E. L. MILOSLAVICH.

METHODS OF PERFORMING ILLEGAL ABORTIONS. M. MAGID and M. WENZKOWSKY, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **19**:501, 1932.

A statistical study is made of 891 women with a history of 4,264 abortions, 133 of which were self-induced and 114 of which were performed by lay people. As to the technic applied, the cases are divided into five main groups: (1) external methods (hot baths, abdominal massages and the deliberate lifting of heavy objects); (2) peroral methods (ingestion of various drugs and poisons); (3) vaginal methods, such as douches; (4) intra-uterine methods (irrigations and foreign bodies), and (5) curettement. Various intra-uterine procedures were the most frequent, even in self-induced abortions (43 per cent), and were constantly employed by midwives, doctors and lay people. Introduction of a catheter or bougie was practiced in 42.4 per cent of the cases, and irrigations with, or injections of, soap solutions in 11.7 per cent. Quinine was taken perorally in 5.3 per cent.

E. L. MILOSLAVICH.

INFANTICIDE BY NEEDLE PUNCTURES. A. UCKE, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **19**:508, 1932.

A 20 year old girl thrust sewing needles and safety pins into her 10 day old illegitimate baby, causing its death from septicemia with purulent pericarditis and bilateral pleurisy ten days afterward. A fragment of a sewing needle was found protruding into the right ventricle of the heart, and the eye-end of another needle was projecting above the external surface of the left lobe of the liver. The broken-off point of a safety pin was found free in the exudate of the left pleural cavity, while another broken-off safety pin lodged within the lower lobe of the right lung. The microchemical examinations of the injured tissues proved the presence of iron particles.

E. L. MILOSLAVICH.

SUICIDE BY SELF-MUTILATION AND DROWNING. JACOBI, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **20**:64, 1932.

A farmer's wife completely severed her left hand at the wrist line with a hatchet and then drowned herself in manure-water. Inside the barn, a blood-stained wooden chopping-block, on which she had rested her left arm, the bloody hatchet, and the cut-off left hand were found. On the volar ulnar aspect of her left forearm, five additional deep cuts were evident. Self-mutilations of this kind may mislead one into assuming that the person has been murdered.

E. L. MILOSLAVICH.

EXTENSIVE ENCEPHALOMALACIA FOLLOWING TRAUMATIC LACERATION OF THE COMMON CAROTID. E. SCHWARTZ, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **20**:67, 1932.

A 39 year old woman sustained, in an automobile accident, a deep tear on the left side of the neck, and the left common carotid was completely severed.

One hour after ligation of the artery and vein, a left-sided hemiplegia developed, and death ensued after two days. Within the left cerebral hemisphere an extremely large area of softening extending up to the brain cortex was found. Thrombotic and embolic processes were absent, and the blood vessels did not exhibit atherosclerotic changes.

E. L. MILOSLAVICH.

HISTOLOGY OF ELECTRIC CURRENT AND LIGHTNING MARKS. M. NIPPE, *Virchows Arch. f. path. Anat.* **285**:1, 1932.

In the mark made by the electric current in the skin when uncomplicated by actual burning, the epidermis contains cleftlike spaces and groups of small rounded spaces separated by a fine meshwork; the epithelium is clumped, and groups of the cells of the malpighian layer have a palisade arrangement and an altered direction. These changes, which are characteristic, Nippe ascribes to the action of heat, which drives water out of the cells. The altered direction of the cells of the malpighian layer is not due to the course of the current, as claimed by some, but to wavelike physical alterations brought about by the current, such as may occur in a wire when a strong current is sent through it. The mark made by lightning differs grossly from that made by the electric current. The former consists either of a group of numerous, closely placed, minute, hemorrhagic points, from which the surface epithelium has disappeared, or of fine, branching, dendritic streaks. Histologically, the difference between the two kinds of marks is even more striking. In the case of lightning stroke, described in considerable detail by Nippe, there was no burning of the skin or singeing of the clothing, although the felt hat worn had been torn to shreds. There were numerous lightning marks on the right side of the body. In the marks the superficial portion of the epidermis had been separated from the deeper portion, but neither part of the epidermis revealed the changes characteristic of the current mark. The capillaries of the corium were engorged, and there were minute areas of hemorrhage. The dilatation of the vessels is ascribed to paralysis of the vessels, and the hemorrhages to tearing of the vessels. Nippe believes that the histologic differences between the current mark and the lightning mark are due to the much greater intensity and the much shorter duration of the application of the lightning current. In the reported case of death due to lightning, except for the lightning marks and petechiae of the eyelids, sclera and pleura, the gross and microscopic observations were entirely negative. The immediate cause of instantaneous death from electric shock or lightning is asphyxia, but whether this is due primarily to cessation of the heart action or to cessation of respiration cannot be determined.

O. T. SCHULTZ.

RUPTURE OF THE HEART IN FALL FROM HEIGHT. O. BERNER, *Norsk mag. f. lægevidensk.* **93**:833, 1932.

A man, aged 28, fell from the fourth floor to the ground; death was almost immediate. A rupture about 9 cm. long, parallel to the axis of the heart, was found in the left ventricle of the heart; the edges were sharp and without extravasation of blood. The diaphragm was perforated. The rupture is explained by hydrodynamics. In this instance the possibility of a bone fragment as the cause of the rupture of the diaphragm and heart was excluded. The rupture of the diaphragm occurred where the heart in its upright position rests on the diaphragm; the patient fell on his chest, and the thorax, because of the fracture of the clavicles and of ribs on the left side, may be assumed to have been comparatively easily pushed in from above downward and toward the spinal column. It is therefore concluded that the heart caused the rupture of the diaphragm, and then directly afterward was itself ruptured, owing to the pressure. Other observations were a fracture of the base of the cranium and particularly of the frontal bone, and hemorrhages both in the lateral ventricles and in the fourth ventricle, and characteristic ecchymosis over the left nucleus caudatus.

Society Transactions

BUFFALO PATHOLOGICAL SOCIETY

Regular Meeting, Dec. 17, 1932

KORNEL TERPLAN, *President, in the Chair*

DIFFUSE SARCOMA OF THE DURA MATER WITH UNUSUAL RESTRICTION OVER A SINGLE HEMISPHERE. J. LANG.

An 11 year old white boy was admitted to the Buffalo City Hospital on March 11, 1932, with a history of a sudden attack of severe frontal headache, nausea and projectile vomiting, followed by delirium, rigidity of the neck and inability to use the fingers of the left hand. The knee jerks were hyperactive, and the Brudzinski, Babinski and Kernig signs were elicited bilaterally. The spinal fluid was clear and under a pressure of 40 mm. of mercury. The patient was discharged after eighteen days' observation. For two weeks he remained without symptoms. One month later he was seen complaining of headache. There was a reduction of vision in the left field, with beginning atrophy of the disk. Three months after the first admission he was readmitted because of atrophy, persistent headache, sleeplessness and vomiting. The fundi showed the effect of increased intracranial pressure. Daily spinal puncture gave relief. The fluid was always clear; the pressure ranged from 20 to 50 mm. of mercury. The condition became progressively worse, the patient dying four months after the first admission.

At autopsy the right parietal bone showed two well defined thinned transparent areas, each measuring 6 cm. across. A tumorous proliferation was noted on the inner surface of the dura, involving the entire right side and measuring from 4 to 8 mm. in thickness. Its surface was dull gray, irregular and nodular. This thickened area tapered gradually at the periphery. Medially it terminated from about 5 to 8 mm. from the falx cerebri; laterally and inferiorly, at the level of the floor of the anterior and middle cranial fossae. There were also two discrete white nodules measuring 4 mm. in diameter on the anterior portion, and 3 mm. on the posterior portion, of the adjacent side of the falx cerebri. On section the tumor was gray and homogeneous. The underlying cerebral convolutions were flattened and showed several white areas, which on section proved to be small tumor masses grouped around blood vessels. There was slight narrowing of the right lateral ventricle and dilatation of the left. Other postmortem observations were not remarkable.

Microscopically, the tumor was a primary alveolar sarcoma of the dura mater, showing a fine stroma in which were embedded masses of cells of alveolar structure. These cells were uniform in size and had large nuclei and a narrow rim of cytoplasm. The stroma was made up of fine interlacing strands of connective tissue, and was quite vascular. Sections from the white areas of the cerebrum revealed a thick layer of tumor spreading along the vessels, leaving the lumens and large areas of brain tissue between the vessels free. No nerve elements or glia were demonstrated by various special methods. The brain was apparently involved by direct contact.

DISCUSSION

K. TERPLAN: The extension of this tumor resembles somewhat a primary sarcoma arising in the leptomeninges, a malignant neurogenous tumor or glioma of the retina, which often show diffuse invasion of the entire subarachnoid space. The gross specimen in Dr. Lang's case indicates clearly the primary origin in the dura mater. The histologic picture is well in line with this conception. The small round cells resemble somewhat the endothelial cells in meningiomas. But

here the more diffuse sarcomatous structure seen in alveolar sarcoma is present rather than the typical picture of meningioma.

I recall a primary round cell sarcoma of the dura mater, which I examined post mortem in Dr. Ghon's Institute in Prague, in a white man. The tumor originated in the right medial fossa and only locally invaded the temporal lobe as well as the underlying bone.

ANOMALOUS DRAINAGE OF THE PULMONARY VEINS IN THE PORTAL SYSTEM, AND OTHER CONGENITAL MALFORMATIONS OF THE HEART COMBINED WITH SITUS TRANSVERSUS. K. TERPLAN and WINFIELD L. BUTSCH.

A white girl lived nine and a half hours after birth. She was intensely cyanotic. Oxygen and digitalis were administered but to no avail. The clinical diagnosis of congenital cardiac disease was made by Dr. F. C. Goldsborough. The anatomic diagnosis was: mirror image situs transversus, transposition of the great vessels, patent septum primum et secundum, persistent left superior vena cava, anomalous drainage of the azygous vein into the left superior vena cava, cor triloculare biatriatum, complete stenosis of the pulmonary artery, anomalous drainage of the pulmonary veins into the portal circulation, an anomalous celiac artery, mesenterium commune and an exceptionally hypoplastic lentil-sized spleen.

The complete absence of pulmonary veins entering the left atrium was the most unusual finding. No veins were seen at any place on the anterior aspect of the atria or ventricles, nor were any noted entering the venae cavae. On the posterior surfaces four veins were seen coming from the upper and lower lobes of both lungs, uniting to form a common trunk which was about 8 mm. in circumference and lay to the right of the vertebral column. There were three branches, one to the esophagus, a large one to the stomach and a third to the region of the duodenum. The lungs showed a marked degree of alveolar and interstitial emphysema. The surface of both lungs was glistening and covered with fine dewlike vesicles.

Only one similar case was found in the literature, that reported by C. H. Hu (*Am. J. Path.* 5:389, 1929). In this case the pulmonary artery, although hypoplastic, was still patent. The anomalous drainage of the pulmonary veins in the portal system was essentially the same. In Hu's case the spleen was entirely absent.

A complete report of this case will be published later.

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY; MYOCARDIAL DEGENERATION AND FIBROSIS OF THE LEFT VENTRICLE, WITH A PARTIAL ANEURYSM AT THE APEX. S. SANES and F. E. KENNY.

An Italian girl, aged 3 months, was admitted to the Children's Hospital, Nov. 1, 1932, because of vomiting of three weeks' duration. Shortly after the onset of emesis, which occurred two or three times a day, cough appeared. Three days before the patient's admission to the hospital breathing became difficult and rapid. The child was born at full term and weighed 7 pounds (3,175 Gm.). No cyanosis was noted at or after birth. Examination showed: temperature, 97 F.; pulse rate, 140; respirations, from 40 to 50; retraction of the intercostal spaces bilaterally on inspiration; dulness throughout the whole left side of the chest with râles. The heart was markedly enlarged; no murmurs were heard; the sounds were distant. The liver was palpable. Within several hours after admission to the hospital, the child died. Necropsy revealed: an anomalous origin of the left coronary artery from the pulmonary artery; marked fibrosis and calcification of the left anterior papillary muscle; fibrosis of the myocardium of the left ventricle with a partial aneurysm of the anterior wall at the apex and septum; marked dilatation of the left ventricle with distinct hypertrophy of its wall, especially toward the base (weight of the heart, 95 Gm.); distinct fibrosis of the endocardium of the left ventricle and atrium; parietal thrombi of the left ventricle; moderate hydroperi-

cardium; slight passive congestion of the liver and kidneys; compression atelectasis of both lungs with lobular pneumonia in the left upper lobe; a low position of the diaphragm; a concave depression in the superior surface of the left lobe of the liver, and a bulging deformity of the left thoracic wall. The foramen ovale and ductus arteriosus were closed. Except for the abnormality mentioned, the coronary vessels were normal. The line of ossification was regular. The histopathologic changes were restricted to the left ventricle. They consisted of endocardial fibrosis, various types of myocardial degeneration, necrosis, reactive cellular inflammation, fibrosis and calcification.

A thorough search of the literature disclosed only five similar cases. The pathologic observations were traced to the anomalous origin of the left coronary artery from the pulmonary artery with resultant anoxemia of the myocardium of the left ventricle. The left ventricle was supplied by venous blood. Whether carbon dioxide in excess had a specific detrimental effect on the heart was difficult to judge. As an embryologic explanation, Abrikosoff suggested that if the anlage of the left coronary artery took origin in the thickening of the aortic bulb at the left, slightly anteriorly to the usual site, the orifice would be incorporated in the pulmonary artery above its left valve after complete formation of the aortic septum, dividing the bulb into aortic and pulmonary trunks.

(A complete report of this paper will appear in the *American Journal of Diseases of Children*.)

CEREBRAL ARTERIES IN RELATION TO ARTERIOSCLEROSIS. C. R. TUTHILL.

A complete report of this paper will be published in the ARCHIVES.

LYMPHOSARCOMA OF THE RETICULUM CELL TYPE. MARGARET WARWICK.

Three cases of lymphosarcoma of the reticulum cell type were presented. All three growths had several characteristics in common. Each was composed of large cells with pale vesicular nuclei and a moderate number of mitotic figures. Also present were numerous large multinucleated cells with similar nuclei but practically no lymphocytes. Each of the tumors arose in a group of lymph nodes, and showed metastases to organs other than lymph nodes. In each case but one group of nodes was involved, and death was caused by progressive cachexia.

The outstanding gross features of the tumors were given briefly:

CASE 1.—In a man, aged 66, the primary tumor arose in the mediastinal lymph nodes with invasion of the right lung. This mass was firm, white and large, practically filling the right pleural cavity, compressing the superior vena cava and infiltrating the right auricle with complete penetration of the wall and the formation of tumor nodules on the inner surface. Metastases could not be demonstrated except in the left kidney, which retained its shape but which was entirely infiltrated with the tumor cells. Some of the glomeruli and tubules were still visible in the masses of tumor cells.

CASE 2.—In a man, aged 50, the primary tumor arose in the retroperitoneal lymph nodes on the right side, forming a soft, bulky, lobulated white mass which appeared to be invading the adjoining structures. The metastases were all in the bones and were demonstrated in the spine, sternum, ribs and femur. Although bulky soft tumors surrounded the bones at the sites of the metastatic tumors, roentgenograms showed no replacement of the bone. Instead, as demonstrated by microscopic sections, the tumor cells filled the haversian canals and infiltrated the bone without destroying its structure.

CASE 3.—In a boy, aged 13, the primary tumor arose in the mediastinal lymph nodes, giving an appearance similar to that in case 1. It was a very firm, white mass which invaded the left lung and filled the entire pleural cavity. The only metastatic tumor was a small nodule, about 2 cm. in diameter, in the lower lobe of the right lung.

DISCUSSION

K. TERPLAN: I think that a careful histologic analysis usually enables the pathologist to differentiate between special types of lymphosarcoma and other conditions producing grossly almost identical pictures, such as Hodgkin's disease and so-called Hodgkin's sarcoma. Recently, in Germany, Roulet applied the term "retothelial sarcoma" to lymph node tumors of the reticulum cell type. It may be said, however, that from Roulet's description it is not altogether clear whether all the cases presented in his first paper were those of reticulum cell sarcoma. Complete postmortem examination sometimes changes the diagnosis made originally from observations at biopsy. In about twenty cases examined in the past two years in our hospital it was possible to distinguish histologically between lymphosarcoma and Hodgkin's disease.

Regular Meeting, Feb. 11, 1933

KORNEL TERPLAN, *President, in the Chair*

SICKLE CELL ANEMIA WITH AUTOPSY. NORMAN HEILBRUN.

A Negress, aged 50, was taken ill with chills, fever and a productive cough ten days' prior to admission to the hospital. Her past history revealed that she had pains in the joints as a child, and ten years before admission had two attacks of a condition called rheumatic fever. There was no history of any familial dyscrasias of the blood.

On admission, the temperature, pulse rate and respirations were elevated. The patient was of short stature and quite obese. The chest showed signs of consolidation at the base of the right lung with many moist and sibilant râles. The heart was enlarged to the left, and the blood pressure was 206 systolic and 120 diastolic. There were no ulcerative lesions found on the extremities.

There were 3,100,000 erythrocytes, with 42 per cent hemoglobin (Newcomber), and 32,000 leukocytes, with a marked predominance of the polymorphonuclears. The fixed smear showed marked variation in size and shape, with much achromia and 80 per cent nucleated erythrocytes. An occasional sickle cell was seen. The reticulocytes were 20 per cent. Wet films showed complete sickling in from four to six hours. The van den Bergh reaction and icteric index were normal; the urobilinogen was not increased. The fragility of the erythrocytes ranged from 0.44 to 0.2. A normal control ranged from 0.44 to 0.32. The Kahn test was negative. Pneumococci found in the sputum were type IV. The other laboratory findings were normal. The clinical diagnosis was bronchopneumonia and sickle cell anemia.

Shortly after admission the symptoms cleared, and the leukocytes decreased to 14,000, the polymorphonuclears still predominating. On the eleventh day after admission, signs of pneumonia again appeared. The patient was placed in an oxygen tent. After five days in the tent, sickling was not evident in wet films until thirty-six hours' after the films were made. Subsequent attempts to produce this effect in a similar manner on the son who has the sickle cell trait failed. The patient died sixteen days after admission.

Autopsy was performed by Dr. Kornel Terplan. There were: bronchopneumonia of the right lower lobe with recent pleuritis; a chronic splenic tumor with thickening of the capsule, the weight being 350 Gm.; hyperplasia of the bone marrow; hypertrophy of the left ventricle with slight fibrosis, and slight hemosiderosis of the liver. The anatomic diagnosis was bronchopneumonia and sickle cell anemia.

Microscopic examination showed several interesting changes. In the spleen, the malpighian bodies were almost completely lacking. The pulp was engorged with great masses of sickle-shaped erythrocytes, while the sinusoids were relatively

empty. Most of the arterioles had moderate hyaline thickening. Here and there was slight fibrosis of the reticulum fibers of the pulp. With an iron stain there were many pigmented endothelial cells, especially around the trabeculae and in the subcapsular spaces. Smears of the bone marrow showed a marked predominance of myelocytic elements with many normoblasts and an occasional megaloblast.

The liver showed slight atrophy of the cords with sinuses filled with sickle-shaped erythrocytes and slight periportal round cell infiltration. The Kupffer cells contained many pigment granules, and an occasional cell showed phagocytosis of erythrocytes. Scattered throughout the parenchyma were small proliferations of endothelial cells, some of which showed pigmentation and phagocytosis. With the iron stain most of the Kupffer cells showed distinct pigmentation.

The reticulum cells of the lymph nodes showed distinct proliferation with occasional phagocytosis of erythrocytes and some deposits of hemosiderin.

In the kidneys there were mild vascular changes. In many of the fibrotic areas was a marked exudation of polymorphonuclears—an acute interstitial nephritis. This was most likely due to the terminal infection.

This case presented the interesting changes of distinct focal endothelial cell hyperplasia in the liver and acute interstitial nephritis in addition to the typical pathologic changes of sickle cell anemia.

CIRRHOSIS OF LIVER FOLLOWING MILD TOXIC DYSTROPHY (SO-CALLED CATARRHAL JAUNDICE) SIX YEARS PREVIOUSLY. RAYMOND S. ROSEDALE.

Autopsy on a woman, aged 23, showed toxic cirrhosis of the liver with huge nodules of regenerative hepatic cells. Inquiry of the parents revealed that when 17 years of age the deceased suffered upper abdominal distress followed by intense jaundice, which persisted for about six weeks. The urine was said to have been coffee-colored. The patient was not hospitalized. The entire period of illness embraced about three months. Since that time her health had been good. She had married within the last year. Three days before her death she became dizzy and vomited a slight amount of blood. Following a large hematemesis, she died unexpectedly.

At autopsy the peritoneum was found to be distinctly wet with a slight amount of free fluid in the pelvis. The liver weighed 725 Gm.; the surface showed hazelnut-sized nodules with intervening, depressed, firm areas. Some areas showed lobular structure of the liver with congestion of the central zone. The cut surface exhibited irregular bile-stained nodules of the parenchyma of the liver surrounded by fibrous stroma. The consistency on palpation was more nearly like that of a normal liver, being somewhat flaccid with wrinkling of the surface, in sharp contrast to the more unyielding character in Laënnec's cirrhosis.

The spleen weighed 200 Gm. and was firm. The veins of the lower part of the esophagus were tortuous, enlarged and thin-walled. A minute erosion was found that admitted a probe.

Microscopically, the liver revealed the changes of a typical chronic dystrophy or toxic cirrhosis (Mallory) with huge nodules of regenerative hepatic cells, collapse of the hepatic stroma and numerous bile ducts.

DYSTROPHY OF THE LIVER IN A TABETIC PATIENT AFTER THERAPY WITH ARSPHENAMINE. S. SANES.

A white man, aged 39, complained of urinary frequency and incontinence, and pain in both legs for one year. He also suffered with epigastric pain and emesis. He said that he had never had a penile lesion. The pupils were fixed. Deep reflexes could not be elicited in either leg. The Romberg sign was positive. The Kahn test of the blood and the spinal fluid gave positive results. The clinical diagnosis was tabes dorsalis and peptic ulcer. The patient received 0.4 Gm. of arspenamine on July 27, and Aug. 3, 1932. A severe reaction with fleeting jaundice

followed the second dose. On August 10 and 17, 0.3 Gm. of silver arsphenamine was given in split doses. Transient jaundice again appeared. The administration of silver arsphenamine, 0.3 Gm., was continued for three doses. Fifteen doses of bismocymol, 1.5 cc., were administered from September 21 to December 7. Acute jaundice developed on December 7; the liver was palpable three fingerbreadths below the costal margin. The laboratory findings included urobilinogen, positive in a dilution of 1:10; dextrose, 98 mg. per hundred cubic centimeters; urea nitrogen, 15 mg. per hundred cubic centimeters; immediate van den Bergh reaction, positive, 25 units; icteric index, 100 plus. Duodenal drainage was negative for pathogenic bacteria. A twenty-four hour sample of urine contained from 16 to 20 mg. of arsenic. Approximately four weeks after the onset of jaundice the skin was clear; the liver was not palpable. The urine showed no bile. The van den Bergh reaction was less than 0.6 units. The patient died on Jan. 28, 1933, from bleeding gastric ulcer and ascending pyelonephritis.

The gallbladder and bile ducts were free. The liver weighed 1,000 Gm. Its margins were sharp. In the right lobe was found a dime-sized, circular, grayish-red area showing no lobular structures. The remainder of the liver presented normal markings.

Histologically, the lobules showed uniformly distinct degeneration of the hepatic cells in the paracentral zone with necrosis. The cells contained greenish-brown pigment which proved to be bile and partly hemosiderin. The central veins appeared dilated. The paracentral reticulum was collapsed following the disappearance of the hepatic cells. In other parts of the lobules regressive changes were also noted. The Kupffer cells were distinctly swollen. The small focal area noted grossly in the right lobe showed nodular regeneration of the hepatic cells, proliferating bile ducts and fibroreticular scarring.

The similarity between the changes in the liver in this case and those seen in a case of jaundice following immediately after the injection of arsphenamine was suggested. Attention was called to the discrepancy between the results of various tests for hepatic function and the actual presence of hepatic damage, as shown in this case.

INGUINAL LYMPHOGRANULOMA. K. TERPLAN.

The histologic sections in two typical cases of inguinal lymphogranuloma were presented, and the differential diagnosis was discussed. Both cases were seen in Buffalo in the fall of 1931. The nodes were excised surgically. In the first case the gross appearance of resected inguinal nodes suggested the correct diagnosis. Smears taken from abscesses revealed no micro-organisms. The second case was seen clinically with bilateral enlargement of the inguinal nodes and acute inflammation of the skin overlying them.

It is believed that the diagnosis of inguinal lymphogranuloma can be made with certainty by histologic analysis. While some areas showed structures similar to epithelioid tubercles, the abscess formations with marked necrobiotic changes in degenerating epithelioid cells and the absence of true caseation spoke in favor of a diagnosis of inguinal lymphogranuloma rather than of tuberculosis. In addition, the diffuse infiltration of the lymphoid structures between abscesses was more multiform than is usually seen in tuberculosis. Often plasma cells, and especially mononuclear giant cells resembling pictures in Hodgkin's disease, were seen about the abscesses. Examination of different parts of lymph nodes must be made, for some sections may show only nodular structures with epithelioid cells in which necrobiotic disintegration and abscess formation have not yet taken place. And here the condition may easily be mistaken for tuberculosis.

Material obtained from the second case was injected into five guinea-pigs. All reacted after a few days with distinct swelling in the area in the abdominal wall into which the injection was made, but without remarkable involvement of the lymph nodes. These experimentally produced infiltrates ranged from the size of a hazelnut to that of a plum. After from ten to fourteen days, they retro-

gressed gradually and finally disappeared. Second transmissions were made from the acute infiltrates without other effect than a slight local reaction. The guinea-pigs were observed from four weeks to one year. Autopsy did not reveal a spread to the lymph nodes. There was only a localized reaction in the abdominal wall, the histologic picture of which appeared as a simple foreign body reaction. Two rabbits were also given injections, but showed no reactions. These observations do not confirm the work of K. Meyer and H. E. Anders, who felt that it is easy to produce experimentally inguinal lymphogranuloma in guinea-pigs and that the spread of the infection closely resembles that of tuberculosis.

The Frei test was made in the first case one year after removal of the nodes, and a distinctly positive reaction was obtained. The second patient could not be obtained for the test.

CEREBRAL ANEURYSMS IN RELATION TO ARTERIOSCLEROSIS. C. R. TUTHILL.

This paper will be published in full in a later issue of the ARCHIVES.

PRIMARY SARCOMA OF THE GREAT OMENTUM. S. SANES and F. E. KENNY.

The clinical, operative and postmortem observations in three cases of primary sarcoma of the great omentum were presented. In 1930, Grieg referred to fifty-seven authentic cases of this disease, reported in the literature.

CASE 1.—A white boy, aged 16 years, complained of pain in the upper part of the abdomen and loss of weight for several months. In the left side of the hypochondrium, palpation revealed a lemon-sized mass which was firm, irregular, movable and tender. Laparotomy disclosed a huge quantity of bloody fluid in the abdominal cavity. A soft, irregular, circumscribed tumor, 14 by 11 by 12 cm., in the great omentum was removed. This growth was bluish red and distinctly cystic. The histologic diagnosis was reticular cell sarcoma with many multipolar cells showing threadlike cytoplasmic radiations and with numerous mononuclear and polynuclear giant cells. The patient died shortly after operation from intra-abdominal fetid abscess in connection with a sinus in the transverse colon, streptococcic thrombophlebitis of the superior vena cava, multiple emboli in branches of the pulmonary artery, infarctions of the lungs and soft splenic tumor. Microscopically, a remnant of the tumor was found in the mesentery.

CASE 2.—A white man, aged 48, consulted a physician because of severe abdominal pain, nausea and emesis of five days' duration. The abdomen was distended and tympanitic; no mass was felt. The temperature was 99 F. Laparotomy revealed about 800 cc. of foul-smelling, purulent material in the peritoneal cavity. The great omentum was adherent to the abdominal wall and viscera. About 50 Gm. of tissue was removed. This specimen consisted of many small nodules of growth which was firm but friable. The histologic diagnosis was large spindle cell sarcoma. The patient died twelve days' postoperatively. Autopsy showed remnants of a primary spindle cell sarcoma of the great omentum, sarcomatous adhesions to the ileum, solitary metastasis to the liver, fetid intra-abdominal abscess in connection with a sinus in the ileum, fibrinous peritonitis and bronchopneumonia of both lungs.

CASE 3.—A white woman, aged 66, complained of progressive enlargement of the abdomen for six months. The abdomen was markedly distended; the superficial veins were dilated, and fluid was present. No mass was felt. Death occurred suddenly four days after admission to the hospital. Autopsy revealed diffuse endothelioma apparently originating in the great omentum, with dissemination to the mesentery, serosa of the gallbladder, parietes, uterus, diaphragm and left pleura. Hemorrhagic ascites and hemothorax in the left side were present. Death occurred from pulmonary embolism.

The first case is of surgical importance because it suggests that early excision of circumscribed tumors might afford a favorable prognosis.

NEW YORK PATHOLOGICAL SOCIETY

*Anniversary Meeting, Jan. 26, 1933*PAUL KLEMPERER, *President, in the Chair*

OBSERVATIONS ON THE RETICULOCYTES OF PIGEONS. ELIZABETH N. DAVIDSON.

Studies of the reticulocytes were made on pigeons' blood. The method consisted in diluting the blood with a vital stain (azure B), allowing it to stand for twenty minutes, preparing a dry cover slip of smears from the dilution and counter-staining with tetrachrome. It was found that less than 1 per cent of the red cells of pigeons are nonreticulated, and that the reticulation occurs in an infinite number of degrees varying from a barely perceptible amount to an almost complete filling of the cell. There occurs only one type of reticulated cell which can be definitely distinguished from the others by the fact that its reticulum appears as a halo about the nucleus. This cell maintains a fairly constant incidence, averaging 8.7 per cent, with variations from 7 to 10 per cent. An attempt is being made to study the possible change in the percentage of occurrence of this type of cell after feeding and after the injection of liver extract.

CONGENITAL ABSENCE OF THE VERMIFORM APPENDIX. SOUTHGATE J. GREEN and WILLIAM J. ROSS.

Green and Ross report a case in which the absence of the appendix was well established by laparotomy, performed because of a clinical diagnosis of acute appendicitis, and by detailed histologic studies following postmortem examination. On the basis of their thorough study of this case, a review of the literature, and some personal observations, they point out: (a) the difficulty of proving true agenesis of the vermiform appendix at operation, (b) the possible unfortunate results of too diligent operative search for this organ, and (c) the desirability of distinguishing between hypoplasia and agenesis. The number of reported cases of agenesis of the appendix is estimated at 26 (21 additional cases reported as instances of this condition are unacceptable either because of lack of proof or because they were instances of hypoplasia). The pathologic changes responsible for the symptoms and signs of acute appendicitis in the case studied were not ascertained.

DISCUSSION

ALFRED PLAUT: What was the cause of the original acute illness which led to the operation?

SOUTHGATE J. GREEN: We examined the gastro-intestinal tract, the genito-urinary tract, the pancreas and the gallbladder, endeavoring to determine the factor responsible for the pain, but were unable to do so. We also asked Dr. Spain, of the clinic for the treatment of patients with allergy, of the New York Post-Graduate Medical School and Hospital, whether the pain might have been due to food poisoning. The patient said that he had had an acute attack of pain, a year previously after eating canned corn and that he had not eaten this food again until just before the onset of the present illness, which seemed to him to be similar to the first attack of pain except that it was more severe. Dr. Spain said that the only evidence of food poisoning that would be demonstrable in the sections would be an increase in the eosinophils, and this we were unable to detect. We were therefore unable to ascertain the cause of the illness which led to the operation.

GAUCHER'S DISEASE WITH UNUSUAL TERMINAL FEATURES. LOUISE H. MEEKER and SAMUEL J. BOCHNER.

In a case of Gaucher's disease in which autopsy was performed there was a history of splenomegaly of long duration.

A Jew, 65 years of age, had been examined thirty-five years before admission to the hospital and was told that he had an enlarged spleen. At that time, the blood picture, including the platelet count, was normal. After about thirteen years with no improvement, roentgen therapy was given for one year. Burns developed in the skin over the area treated, and treatment was discontinued. The ulcerated areas were a source of discomfort until death. This largely overshadowed the distress caused by the "pressing weight" of the enlarged spleen.

The patient came to the New York Post-Graduate Medical School and Hospital on Oct. 25, 1932, complaining of severe attacks of biliary colic which had begun a month previously. Cholecystotomy with removal of gallstones was done. The surgeon noted many gray and red nodular masses in the massively enlarged spleen and liver and suggested a diagnosis of metastatic carcinoma. Biopsy specimens were taken from a nodule of the liver and from the lesions of the skin. The pathologist reported chronic nonmalignant ulcer of the skin and reticulo-endothelial lipomatosis of the liver (Gaucher). Two days later the patient died. The blood, even during the last illness, was fairly normal. Among the cases of Gaucher's disease that have been reported we have found but one other case in which roentgen therapy was used on the basis of an empiric diagnosis of splenomegaly. Irradiation was without effect in that case also.

Necropsy, limited to the region about the abdominal incision, was performed forty minutes post mortem. The body was well developed. General icterus was marked. Pingueculas were not present. The abdominal skin in the splenic region showed ulceration and cicatrization. The superficial lymph nodes were not palpable. There was no gross evidence of a pathologic process in the bones. The spleen weighed 4,635 Gm. The surface was bossed by rather irregularly rounded red to yellow nodules. The cut surface was rather dry and the scrapings were cell-poor. The characteristic architecture of the spleen was not recognizable. The liver weighed 3,570 Gm. The surface was bossed by small and large rounded, yellowish masses, in part isolated and in part confluent. The cut surface presented numerous large and small yellow masses, the largest of which showed central hemorrhages. The substance of the liver was firm and presented the picture of biliary cirrhosis. The mesenteric lymph nodes were soft and freely movable. The largest of these measured 10 mm. in diameter. The cut surface was yellow.

The structure of the spleen, liver and lymph nodes showed extensive replacement of the normal elements by the large pale cells of Gaucher's disease. Many of these cells were multinucleated and measured from 20 to 75 microns in diameter. Large cell masses were occasionally noted; one, apparently a syncytial mass, measured 350 microns in diameter. The masses formed a prominent part of the picture in all sections of the spleen, appearing as group and islands and in many areas presenting an alveolar arrangement. The pale cells were similar in all respects to those described by Gaucher, Bovaird, Mandelbaum, Schlagenhauser and others, and variously named epithelioid, endothelial, lipid, histiocytic and Gaucher's cells. With Bielschowsky's silver impregnation method the reticular fibrils were seen to surround, and in places appeared continuous with, the substance of the Gaucher cells. Further studies are needed. Smears of the fresh splenic pulp were stained with the tetrachrome stain for blood (fig.). They showed large pale cells, almost equaling the leukocytes in number and varying from 40 to 100 microns in diameter. Many were multinucleated, some having thirty nuclei. Some of the larger cells showed phagocytosis. Sections of the skin of the abdomen showed ulceration and scarring but no malignant process.

The use of special methods for identifying the lipid content of the large clear cells typical of Gaucher's disease yielded nothing more than other observers have reported. These studies indicate that the pale cells of the Gaucher type are filled chiefly by the cerebroside group of lipoids. Stains for iron showed a scant quantity in occasional Gaucher's cells, and in these areas the reticulum similarly showed some iron.

Summary.—This case was proved to be one of Gaucher's disease by the history and the gross and microscopic changes. The picture was obscured by ulceration

of the skin (caused by roentgen therapy) of twenty-two years' standing and by the lack of symptoms other than the cutaneous lesions, as well as by the gross appearance of the spleen and liver at the time of operation. Death was due to intercurrent factors, cholelithiasis and the shock of a major operation. The salient



Smear of fresh splenic pulp stained by the tetrachrome stain for blood. The large pale cells are the Gaucher cells. One on the left side is multinucleated.

features of the history are the patient's race (Jewish), his age (65 years), the splenomegaly of thirty-five years' duration and the absence of changes in the blood. In the microscopic studies special stains and examination by polarized light cor-

roborated the findings of other observers regarding the lipoid content of the Gaucher cells, their iron content, meager in this case, and their relation to the reticulo-endothelial system. The mesenteric lymph nodes were of special importance.

DISCUSSION

PAUL KLEMPERER: In the last six years my associates and I have seen eight patients with Gaucher's disease; four of them died, and four were operated on, so we were able to study the spleen. Reports of five cases have been published by Drs. Oppenheimer, Rosenthal and Welt; three have not been published. One of the latter was particularly interesting, because the condition was accidentally found at autopsy in a man of 72 who had died of carcinoma of the pancreas. His spleen weighed only 500 Gm. The bone marrow showed nests of Gaucher's cells. This case shows that the disease may develop even in the late years of life.

I think that the case presented is interesting because of the correlation of the condition with roentgen treatment; dermatologists agree that roentgen treatment is of little value in Gaucher's disease, and this case proves it.

A. A. EISENBERG: Two weeks ago my associates and I observed a case of Gaucher's disease in a Jewess, 55 years of age; the spleen weighed 7.2 Kg. (about 15½ pounds).

THERAPEUTIC USE OF BACTERIOPHAGE AGAINST COLON BACILLI. WARD J. MACNEAL, FRANCES C. FRISBEE and MARTHA APPLEBAUM.

The development of a bacteriophage against the colon bacillus presents the same problem whether the organism infects the urinary tract, the blood stream or the intestinal tract. The bacteriophage of the colon bacillus has a high specificity. This necessitates the use of a large number of races, each highly potent and multivalent, in the preparation of individual lytic agents for therapy. The individual lytic agents are prepared by adapting a stock race of bacteriophage to the infecting organism. Various principles which must be borne in mind in using this form of therapy are: the necessity for careful control of the hydrogen ion concentration of the infected region; the necessity for close contact between the infecting agent and the lytic agent, and the inadvisability of using antiseptics at the same time that bacteriophage is used.

Four cases of colon bacillus septicemia are reported, with recovery in 3 instances. Colon bacillus bacteriophage in asparagine was injected intravenously. The use of the bacteriophage in colitis was followed by improvement but was not markedly successful. More than 250 patients with acute or chronic pyelitis have been treated with bacteriophage by subcutaneous injection, instillation through the bladder and intravenous injection of the asparagine preparation, in varying combinations. The p_H of the urine was carefully controlled. Clinical success was evident in more than half the cases, and in some instances the results were dramatic.

A bacteriophage which is so active as to cause complete destruction of the organism becomes an effective weapon against colon bacillus infection in any part of the body.

NOTE.—This work was supported by a grant from the Josiah Macy, Jr., Foundation.

STREPTOCOCCUS BACTERIOPHAGE AND STREPTOCOCCUS CULTURE FILTRATES IN THE TREATMENT OF ENDOCARDITIS LENTA. WARD J. MACNEAL, MARGARET E. STRAUB and MARTHA JANE SPENCE.

During a period of eighteen months, seven patients suffering from endocarditis lenta were treated with autogenous filtrates of broth cultures of streptococci to which bacteriophage had been added. Six died, and one is still under treatment. The patients received the culture filtrate and also blood serum from donors who

had been treated with the same filtrate. Apparently the course of the disease was somewhat altered, but there is no reason to claim any success.

NOTE.—This work was supported in part by a grant from the Josiah Macy Jr., Foundation.

THE HEART IN A CASE OF ENDOCARDITIS LENTA AFTER TREATMENT WITH BACTERIOPHAGE. REUBEN MACBRAYER and SAMUEL J. BOCHNER.

A white man, aged 29, who had had attacks of rheumatism twelve years previously, was treated intensively for subacute bacterial endocarditis by subcutaneous and intravenous injections of a culture filtrate of *Streptococcus viridans* which had been inoculated with streptococcus bacteriophage and by weekly transfusions of blood from donors immunized by injections of the same material. After three months' treatment he died. Detailed histologic study of the heart revealed strikingly the following changes, at least some of which are unusual in subacute bacterial endocarditis: (1) an inflammatory process, mainly productive, involving the endocardium; (2) a pancarditis which was traced from the endocardium to and through the epicardium, producing pericarditis; (3) severe myocardial inflammation and degeneration, especially of the left side of the heart; (4) few evidences of the rheumatic lesions, and (5) numerous polymorphonuclear leukocytes and monocytes containing phagocytosed streptococci. We believe that the productive inflammation and phagocytosis were favorably influenced by the therapy.

The paper just presented by Dr. MacNeal and his associates set forth the technic of this therapy and the clinical results in seven patients.

DISCUSSION OF PAPERS ON BACTERIOPHAGE

ALFRED PLAUT: Is there a possible relation between any unusual changes in the heart and the treatment in the case reported by Dr. MacBrayer and Dr. Bochner? Or does the opinion prevail that the same lesions might have been present without treatment with bacteriophage?

PAUL KLEMPERER: The lesions in this case were distinctly productive. However, as the picture in subacute bacterial endocarditis is extremely protean, one might, in studying a number of cases, find identical changes; hence I should not lay too much stress on the lesions in the heart as evidence of the influence of treatment. In fact, subacute bacterial endocarditis is characterized by a much more productive type of lesion than is acute bacterial endocarditis, in which an exudative necrotizing lesion predominates.

Phagocytosis is found in untreated patients as well. The giant cells which one finds frequently in lesions of subacute bacterial endocarditis often contain bacteria.

I feel that one cannot gain much encouragement from the histologic picture in this case; but of course it is one case only, and the clinical features in the other cases are possibly more significant.

GEORGE BAEHR: The work reported has been painstaking, and it has taken courage to reopen the subject of the therapy of subacute bacterial endocarditis. The pathologists with whom I am associated who have been studying the disease for several decades have been discouraged by the monotony of the bad results. Few of us have seen any patients get well. A few cases in which recovery occurred have been reported in the literature, and Dr. Libman has seen patients recover spontaneously, become reinfected and again recover. I have seen one or two patients become bacteria-free spontaneously, and later die from reinfection. We have followed a few hundred cases clinically, and have been fortunate in seeing 170 autopsies; from the latter we have learned little concerning why some patients become bacteria-free. Of the 170 patients that came to autopsy, 59 died in the bacteria-free stage of the disease. The remarkable thing is that every one of the 59 patients became bacteria-free spontaneously, shortly after the onset of the disease. In the rest of the 170 patients, bacteria were constantly in the blood

stream during the many months from the time of infection until death. The patients in whom an infection of the heart valves with anhemolytic streptococci develops are of two types: Either the immunologic mechanism is intact and they become bacteria-free immediately after the onset of the disease, or they never kill all the bacteria on the heart valves. Those who become bacteria-free shortly after the onset of the disease have the same pathologic lesions, the same infarction and the same embolic glomerular lesions as the others. But the embolic glomerular lesions in the kidney are much less numerous, because the infectious stage of the disease has been shorter. The majority of persons in whom the valves of the heart become infected with this organism of low virulence seem to possess no resistance to infection and never kill all the bacteria. The number of bacteria in the circulating blood fluctuates from day to day, depending on the number swept off mechanically from the vegetations, but the total number in the blood stream is kept fairly well in check, possibly by phagocytosis and other methods of removal. As Dr. Klemperer has emphasized, not infrequently there are numbers of phagocytes in the vegetations, and there may also be a great deal of organization in some of the vegetations, particularly when the infection has been present for a long time before death. In spite of the discouraging results which have just been described, and in spite of the fact that the blood stream in the cases reported has not become bacteria-free, it is by some such persistent and courageous effort that the means of sterilization of the blood and of the valves of the heart may eventually be discovered. Unfortunately even this may not be a complete answer to the problem, for all of the 59 patients whom we have seen in the bacteria-free stage of the disease have died as a result of the progressive anemia, of asthenia or of the embolic phenomena of subacute bacterial endocarditis. One third of the patients who became bacteria-free (19 of 59) died in a state of uremia following glomerulonephritis, a complication which rarely occurs in the patients who do not kill all the bacteria.

WARD J. MACNEAL: We undertook to do this work on subacute bacterial endocarditis largely because the work was forced on us. Patients have been referred from other hospitals and sent by physicians who were under the impression that because we had attained some success in the treatment of bacteremias due to staphylococci and the colon bacillus, we might obtain equal success in this field. I am much disheartened by the results in these cases of endocarditis, and I should long ago have refused to undertake the handling of any more cases of this kind had it not been for the enthusiasm of those associated with me. I am grateful to them for their enthusiasm, and I am on my feet to express my satisfaction in being associated with persons who are still willing to tilt at windmills.

Regular Monthly Meeting, Feb. 23, 1933

PAUL KLEMPERER, *President, in the Chair*

PATENT VENTRICULAR SEPTUM WITH MURAL ENDOCARDITIS DUE TO STAPHYLOCOCCUS ALBUS. LAWRENCE H. COTTER.

A patient came to Gouverneur Hospital with a typical picture of sepsis; he had a septic temperature, and showed numerous petechiae, enlargement of the spleen and heart murmurs and a marked thrill in systole and diastole. The heart showed signs of considerable hypertrophy. The rate was rapid. There were a high white cell count and a high polymorphonuclear count. Repeated blood cultures showed *Staphylococcus albus*.

Autopsy showed marked hypertrophy of the right and left ventricles and a round hole in the interventricular septum about 2 cm. in diameter, just below the valve attachments. On the wall of the right ventricle opposite this opening the endocardium was thickened, and there was a cauliflower-like vegetation attached

to the thickened endocardium. This vegetation was very soft, friable and roughly spherical, measuring about 3 cm. in diameter. There were infarcts and small abscesses in the lungs and numerous infarcts in the spleen and kidneys. There was no involvement of the endocardium around the hole in the septum. Dr. de la Chapelle has two specimens with patent interventricular septums and *Streptococcus viridans* at the margins of the openings, but I have seen none like this.

PRIMARY LIVER CELL CARCINOMA. VERA D. DOLGOPOL.

G. M., a white man, aged 83, entered the hospital because of edema of the legs. He died nine days later of a condition that was diagnosed as chronic myocarditis and cirrhosis of the liver.

At autopsy an ascites of 2,000 cc. was found. The liver was diminished in size, but was not cirrhotic. The right lobe, in its upper part, contained a massive necrotic tumor 11 cm. in diameter, with macroscopic extensions; the microscopic structure was that of a primary liver cell carcinoma. Macroscopic thrombi of tumor tissue were present in the portal vein, in the larger hepatic veins and in the small branches of the right pulmonary artery. Tumor nodules measuring up to 1 cm. in diameter were present in the right lung. No abdominal lymph nodes were involved.

Cirrhosis is absent in only 15 per cent of cases of primary carcinoma of the liver.

DISCUSSION

LAWRENCE H. COTTER: Can someone tell me roughly what proportion of these tumors do not show metastases?

VERA DOLGOPOL: Tumor metastases in the lungs occur in about 20 per cent of cases, and at that the lungs are organs in which there is rather frequent microscopic involvement. In general, liver cell carcinoma is not an easily metastasizing tumor.

PAUL KLEMPERER: Two years ago I had an unusual opportunity to observe a primary carcinoma of the liver in a patient who had been given thorotrast. It was most interesting that the Kupffer cells in the cirrhotic part of the liver contained thorotrast, while the endothelial cells within the primary carcinoma did not, a fact which proved the contention that has been held for years, that the endothelial cells within a primary carcinoma of the liver are not of the Kupffer cell type.

A RARE CASE OF ULCERATIVE JEJUNITIS (SYPHILITIC?). S. H. POLAYES and J. R. PEARSON (by invitation).

A white youth, 17 years of age, was admitted to the Jewish Hospital of Brooklyn on Aug. 12, 1932. He had been treated in the outpatient department for a month previously for the following symptoms which had occurred during the past year: abdominal pain, loss of weight, night sweats, a rise in temperature in the evening and, more recently, diarrhea and fecal vomiting. Physical examination led to a diagnosis of tuberculous peritonitis with adhesions, causing intestinal obstruction. The latter was confirmed by roentgen studies. The various laboratory tests (studies and chemical analyses of the blood, Wassermann and Kahn tests and examinations of the stools and urine for parasites, typhoid, dysentery and tubercle bacilli) were negative. The patient was advised to have an operation, but refused. He died on December 12.

Postmortem examination showed the following changes: ulcerative jejunitis with multiple strictures, ascites, fibrosis of the lung, spleen and pancreas and fat replacement of the liver.

The following conditions were excluded by postmortem examination of the tissues and by various clinicopathologic tests: tuberculosis, dysentery, typhoid, parasitic infections (ameba and actinomycosis), Hodgkin's disease and neoplasms (lymphoblastoma, sarcoma and carcinoma). Of the other two possible conditions, nonspecific enteritis and syphilis, the latter was considered to be the more probable

diagnosis because of the striking similarity between the intestinal lesions in this case and those in the previously described authentic cases of syphilis of the intestines. The lesions were described as follows:

The duodenum and jejunum were markedly distended with gas to a point about 15 cm. above the ileojejunal junction. At this point there was an irregular band of constriction in the wall of the jejunum, 2 cm. in width, producing a stricture which almost completely obliterated the lumen of the organ. A similar band of constriction was present distally at the ileojejunal junction. The mucous membrane lining the jejunum was the seat of numerous superficial and deep ulcers, transverse as well as longitudinal to the axis of the intestine. The ulcerative process was most marked in the distal 15 cm. of the jejunum between the two constrictions. Here the chronic ulcerative process had produced bridging of the mucosa and nodular thickenings in the wall, the latter simulating tumors. On section, however, the thickenings were found to be due to chronic inflammatory changes in the wall opposite the ulcers.

Microscopic sections through the jejunal ulcers showed large portions of mucous lining destroyed and replaced by exudate which consisted of fibrin and polymorphonuclear as well as mononuclear and plasma cells. The structure beneath this layer was made up entirely of granulation tissue. This tissue was infiltrated with round cells and plasma cells. There was an accompanying marked fibroblastic reaction. The blood vessels were exceedingly numerous in this area and were thick-walled, presenting marked endothelial proliferation of their intimal linings. The veins as well as the arteries participated in this process. At the junction of the submucosa and the muscularis there were occasional multinucleated giant cells surrounded by round cells. There were no epithelioid cells.

The muscularis mucosae was extremely hypertrophied, and in the ulcerative areas was distorted by the infiltrative and granulomatous changes. Beneath this layer the infiltrate assumed a focal character, forming discrete collections of round cells with a tendency to perivascular infiltration. In some of these lesions there was an excessive amount of scar tissue.

The muscularis and serosa showed a less extensively destructive process, but here also the chronic inflammatory nature of the disease was marked, especially in the serosa, where the tendency to perivascular round cell infiltration was most evident.

Levaditi, Jahnelt and Starry-Warthin stains of the scrapings of the ulcers showed the presence of structures resembling *Spirochaeta pallida*. Acid-fast stains were negative for tubercle bacilli; bacteriologic studies were negative for dysentery and typhoid bacilli. Stains for parasites were negative.

This case is presented as an extremely interesting problem with the purpose of receiving any helpful suggestion so as to arrive at a definite diagnosis.

DISCUSSION

SYLVAN E. MOOLTEN: Would Dr. Polayes be willing to make any estimate of the probable duration of the illness?

PAUL KLEMPERER: Were there changes in any other organ indicative of syphilis?

DAVID PERLA: I listened to the case very carefully. I do not see any evidence of its being one of syphilis. The history is that of a youth of 17. There is no history of syphilis, and the morphology is certainly not in favor of syphilis. I cannot make out from your description, from the histologic preparations or from the lantern slides, and I had occasion to examine the sections, that there is any definite evidence of syphilis. The finding of a few things which may look like spirochetes on the surface smear of the intestinal tract would hardly be convincing. I think that it would be much wiser to diagnose this case as one of chronic ulcerative jejunitis of unknown etiology. There is no crime in not knowing the etiology of a disease; by that I mean that you would be much wiser in limiting yourself to facts and not trying to make a definite diagnosis when no definite diagnosis

can be made. I do not think that any one would be able to make a diagnosis in a case of this type from the postmortem material.

PAUL KLEMPERER: Dr. Polayes is at a disadvantage in not being able to present his evidence in lantern slides as well as by the microscope. We are also at a disadvantage in that we cannot judge from the few photomicrographs presented, but there is a Committee on Microscopy to which I think these sections should be submitted for an opinion.

S. H. POLAYES: With regard to the age of the lesion, from the clinical history, the lesion was active for nearly two years. Of course, if it is syphilitic, it is possible that the condition was hereditary.

In reply to Dr. Klemperer's question concerning the findings in other organs of the body, I believe that the interstitial fibrosis which was found in the pancreas and which we know is not so common a finding in ordinary cases of enteritis might be considered of syphilitic origin. The same may be said of the pulmonary fibrosis. Although neither of these changes can be considered definitely syphilitic, it must be pointed out that in only a few of the so-called authentic cases of syphilis of the intestines were definite evidences of syphilis found in other organs.

With regard to Dr. Perla's comment, I should like to repeat that a definite diagnosis of syphilis was not made in this case, nor was any importance attached to the findings of spirochetes in the smears from the surface of the ulcers. The case is presented for discussion and for any suggestion one may offer as an aid in determining the etiology. Although a diagnosis of syphilis cannot be made with certainty in this case, it must be pointed out that if this is not a case of syphilis, then the etiology of the previously reported cases which were based on the same histopathologic changes as were found in the present case will also have to be doubted. If the previously reported cases can be considered authentic, one cannot exclude the diagnosis of syphilis in this case, in view of the striking similarity between the lesions in this case and those in the so-called authentic cases of syphilis of the intestines.

A LYMPHOCYTE HEMOGRAM. CARL REICH.

Based on the work of Wiseman, who showed that basophilia of the cytoplasm is a constant and reliable criterion of the age of lymphocytes, I undertook a series of studies to see whether a classification of lymphocytes according to the degree of basophilia would be of clinical value. The type of cases selected was widely diversified and represented all types from the very sick to the ambulatory patients with minor complaints. The patients were studied at biweekly intervals during their stay in the hospital. Suitable controls were employed.

Technic.—White and differential counts were made for each observation. The Wright-Giemsa stain was used. The lymphocytes were divided into three classes, Y, M and O, according to the degree of basophilia of their cytoplasm. The Y forms had a deep blue cytoplasm; the M forms, moderately blue, and the O forms, faintly blue or colorless. The percentage of each form was calculated, the procedure being similar to that used in determining the Schilling index. There is a constant lymphocytic formula for normal persons. For adults this can be expressed as Y forms 5 per cent, M forms 50 per cent and O forms 45 per cent. Variations occur in this formula under different conditions, and one can therefore speak of a shift to the left or to the right of the lymphocytic index, depending on whether the number of younger forms is greater or lesser than normal. A comparison with the Schilling index in each case shows that the two do not run parallel. The lymphocytic index is not as stable as the Schilling index and will shift to the left just as easily in a mild as in an acute infection. Even though the lymphocytic formula cannot be used to gage the severity of an infection, its shift to the left in these conditions nevertheless indicates that lymphocytes take an active part in combating bacterial invasion, as is seen by the increase in Y and M forms and the decrease in O forms in practically all cases of infection. The lability of the lymphocytic hemogram makes it valuable in the detection of minor infections which

do not disturb the more stable Schilling index. Interesting and confirmatory evidence for using basophilia as a criterion of the age of lymphocytes is seen in the study of the lymphatic leukemias. In these cases there is a marked increase in the proportion of Y and M forms, indicating the well known hyperactivity of the lymphatic system in this disease. In the myeloid leukemias there are also an increase in lymphocytic activity and a shift of the index to the left. It is of interest to note also that according to the lymphocytic index the period of convalescence is probably much longer than is usually expected.

DISCUSSION

MAURICE MORRISON: I looked very carefully at the first picture showing the different types of cells. There was one cell which showed a marked basophilia but no nucleoli. One large cell had slight basophilia and contained nucleoli. It was my impression that the first cell was an ordinary lymphocyte, while the other one was a lymphoblast. I should not use basophilia alone as an index of youth. I should use it only in conjunction with the other morphologic characteristics of the cell, especially the presence or absence of nucleoli.

ALFRED PLAUT: Has there been any opportunity to examine the lymphocytic index in typhoid fever, or the so-called infectious mononucleosis? Also in case there is a shift in the lymphocytic index in infection, does it prove that they take an active part in combating the invader? It seems to me it shows only that they react.

ARTHUR SCHIFRIN: Was the lymphocytic index studied in any cases of agranulocytic angina?

MAURICE RICHTER: Does Dr. Reich consider all the Y forms, particularly in the normal blood smear, as lymphoblasts? The ones he has in his illustration are apparently of that type. Plasma cells and so-called Türk irritation forms have basophilic cytoplasm, and their presence might cause a shift to the left. I should also like to ask whether there is a shift in noninfectious conditions.

CARL REICH: So far as the question of lymphoblasts and nucleoli is concerned, Naegeli and all the hematologists insist that the chromatin and nucleoli are important in the differentiation of cells. Most of the lymphoblasts show a fairly deep blue cytoplasm, and the Y form—the ordinary deeply stained lymphocytes—are not supposed to be the same age; they are merely younger than those which are very pale.

I think that Dr. Plaut is perfectly right. The shift probably indicates an activity of the lymphocyte, but just what that is, I do not know.

I have not had an opportunity to study agranulocytic angina, nor a chance to study the lymphocytic index in enough cases of typhoid fever. I have had only one case of infectious mononucleosis which was of the monocytoid type. As I did not have an opportunity to study more of these cases, I did not think it fair to say anything about them.

In reply to Dr. Richter's question, I can say that in normal persons and in those with a cold, sinus trouble or arthritis, there was a shift. The point concerning the plasma cells and the Türk irritation forms is important; I do not recall seeing a great many of them. I think that they can be classified with the Y forms.

MAURICE RICHTER: Is there a shift to the left during convalescence?

CARL REICH: I think that there probably is a shift during convalescence.

INTRANUCLEAR INCLUSIONS IN TUMORS OF THE BRAIN. ABNER WOLF.

In studying a series of tumors of the brain during the past year, unusual intranuclear structures were observed in some of the cells in a certain percentage of the neoplasms. The intranuclear bodies resemble in many respects those found in many of the virus diseases. They are acidophilic in staining reaction, have sharp margins,

often have a halo around them and are single or multiple. They vary considerably in size, ranging from 3.5 microns in diameter to 9.7 by 12.7 microns.

In sections stained with hemotoxylin and eosin, the intranuclear structures are seen as eosinophilic rounded masses with distinct contours and often with a thin dark blue rim. The smaller bodies are deeply colored, whereas the larger ones are much paler. They are either homogeneous or finely granular and often show more concentrated central or eccentric areas. In the majority of instances a clear zone or halo is found about them. The nuclear chromatin tends to clump and collect along the nuclear membranes. At times the clear space is not so well defined, the chromatin being irregularly distributed and in contact with the inclusion along a considerable portion of its border. Often the chromatin is very dense and less distinctly particulate and fills almost all of the nucleus about the inclusion. Occasionally only a few chromatin particles are seen between a large inclusion and the adjacent membrane, or the scant chromatin radiates in strands from the inclusion. The nucleoli are basophilic, although at times they too are eosinophilic and have a thin blue margin. At times they are pressed toward the margin of the nucleus, and occasionally they are not found.

The inclusions occur most often in uninucleated or multinucleated giant cells, but they may occur within cells of the whole range of the given tumor. The nuclei containing them may be regular in outline, or they may have wrinkled or serrated margins.

The inclusions are found exclusively within tumor cells and not in the ganglion or glia cells of the adjacent or invaded nervous tissue. Four or five may be found in one low power field, sometimes many within one nucleus, or often only a single inclusion is found in an entire section.

One hundred and sixty-five tumors of the central nervous system were examined: 100 gliomas, 60 mesodermal tumors and 5 tumors of the pituitary body. Twenty-five per cent of the gliomas showed inclusions of the type described. The greatest number was found among the neoplasms classified as glioblastoma multiforme. Thirty-three of these tumors were examined, and 16, or almost half, showed intranuclear inclusions. Four of 17 medulloblastomas, 1 of 28 fibrillary astrocytomas, 2 ependymomas and 1 neuroblastoma showed such intranuclear structures. Sixty mesodermal tumors were examined, and of these 15 showed intranuclear bodies. They were most frequently encountered in the meningeal fibroblastomas, of which 32 were examined, and 9 showed inclusions. Of 12 perineurial fibroblastomas, 5 showed inclusion bodies. None of the adenomas of the pituitary body showed inclusions.

Dorothy Russell in a recent publication reported the finding of inclusions in all essential respects like those reported here in a third of a series of 192 gliomas examined. She stated that "if they indicate a virus infection, it is probable that the virus is the cause of the tumor."

If it is conceded that my inclusions and those described by Russell are the effect of a virus and not merely a degeneration phenomenon in spite of Cowdry's warning "that the presence of intranuclear inclusions in unknown conditions should not be taken at face value as indicating the action of some filtrable virus," their etiologic significance would not yet be established. Rivers and Pearce showed that viruses (virus III and vaccine virus) multiplied rapidly in a transplantable tumor in a rabbit and were carried along with the tumor through an indefinite number of transplantations. Findlay and Ludford reviewed a group of cases in which intranuclear inclusions were found and in which no active virus disease was present. One must, therefore, seriously consider whether the virus present in the tumors of the brain studied is not merely an incidental inhabitant. I believe that it is impossible to say from my finding of intranuclear inclusions in such tumors of the brain that either the gliomas or the mesodermal tumors of the central nervous system are caused by a virus or viruses. Only the production of similar tumors by the filtrate from such tumor material with the reproduction of intranuclear inclusions would be conclusive.

DISCUSSION

DAVID PERLA: I think that intranuclear inclusions are fascinating things. I have seen them repeatedly in many different varieties of conditions. One sees them in all forms of malignant neoplasms. They are frequently seen in squamous cell carcinoma of the skin: eosinophilic inclusions of the nucleus. Many good pathologists have stumbled badly on these intranuclear inclusions and have drawn erroneous conclusions and deductions. The fact that in virus diseases one sees peculiar inclusion bodies, most of which one knows nothing about and does not understand, does not mean that the presence of similar eosinophilic bodies limited to the nuclei in neoplasms bears any relation to virus disease. I think that if one examines a number of conditions other than tumors of the central nervous system, one finds that they bear no definite relationship to tumors of the central nervous system as such. The closing sentence of Dr. Wolf's paper was extremely apropos, and one should be more than cautious in suggesting a relationship of virus diseases to tumors from the appearance of nuclear bodies. Just what they mean is difficult to say, because one does find them in actively growing cells in which there is no evidence of any degeneration, but that they have any significance so far as indicating the presence of a virus condition, either complicating or etiologic, there is no evidence.

S. H. POLAYES: In a case of psittacosis which my associates and I had the opportunity to study, we found inclusion bodies in some of the cells, but they were not necessarily limited to the nucleus. They were in the cytoplasm of the cells as well. While listening to Dr. Wolf's paper, this question arose: Why, if caused by a virus, does the inclusion body always attack only the nucleus? One would expect to find some cells in which the peculiar inclusion body was in the cytoplasm as well as in the nucleus.

ABNER WOLF: I am glad to hear that Dr. Perla agrees with me in my conclusions.

In regard to Dr. Polayes' question, there are virus diseases in which the inclusion bodies are typically only in the nuclei and do not occur in the cytoplasm. The inclusions seen in the neutrophic virus diseases are almost all of that type, and it may well be that if the condition presented is a virus, it is one of that type.

LIPOSARCOMA, INTRACANALICULAR FIBROMA, PERICANALICULAR FIBROMA AND CYSTIC CHANGES OF THE BREAST. MAX LEDERER and (by invitation) SAUL LIVINGSTON.

This case is reported because of its rarity and the multiplicity of lesions in one breast.

A Jewish woman, aged 44, was admitted to the hospital on Sept. 22, 1932. She stated that three weeks prior to admission she noticed a lump in the right breast, which had not increased in size, been painful or throbbled. The skin over it was never red. She does not remember ever having hurt her breast, and no discharge from the nipple was noticed.

Physical examination revealed a rather apprehensive woman in good health. General physical examination revealed nothing abnormal. The nipples were normal in appearance; the breasts were symmetrical. A tumor mass about 5 cm. in diameter occupied the lower outer quadrant of the right breast. The tumor was hard in consistency, moved freely in the breast, felt rather circumscribed and was not attached to the deeper parts. The axillary lymph nodes were not enlarged.

The operative procedure consisted in a thoracomammary incision, exposing the posterior aspect of the breast. A large encapsulated growth was enucleated. The tumor was lobulated, yellowish white and soft. A frozen section showed it to be a liposarcoma. The breast was removed, and the axilla was cleared of all fat and lymph glands. The postoperative course was uneventful except for a rise in temperature of from 1 to 2 degrees on the first and second days. The wound healed well, and the patient was discharged six days after operation.

Four months after operation the patient's general condition was excellent; the scar over the right side of the chest was freely movable, and there was no local recurrence. Roentgen examination of the chest showed no metastasis.

Macroscopic examination of the breast showed it to consist of several portions: (A) There was a tumor which appeared lobulated, was oval, measured 5 by 3 by 4 cm. and was ocher-colored. The consistency was rubbery; the surface was smooth. On section it was seen to be made up of numerous lobules of yellow tissue with a homogeneous appearance. (B) Other portions contained similar yellow tissue, which was softer and more distinctly lobulated. Scattered throughout were smaller nodules of the same appearance. In one portion of the specimen was a papillomatous mass arising by a narrow pedicle from a smooth lining membrane. This mass was translucent and presented a papillomatous appearance. (C) The breast proper contained solid nodules which somewhat resembled the tissue first described. (D) There was fat at the distal points. (E) The lymph nodes were enlarged.

Microscopic examination of the main tumor showed it to consist mostly of cells which varied greatly in size, and in the hematoxylin-eosin stained preparation it appeared mostly as clear spaces surrounded by a delicate cell membrane. Occasionally white trabeculae divided the spaces into two or more compartments; some contained a very delicate fibrillar network. The nuclei occupied various positions in the cell, some being centrally, while others were eccentrically, located. The nuclei varied greatly in size and shape; some were intensely hyperchromatic, and an occasional nucleus showed a mitotic figure. In some instances there was more than one nucleus, while in others the cells appeared to be polymorphic. Scattered throughout were collections of cells with a pink-staining granular protoplasm, some of which contained a few small clear spaces. An occasional giant cell with a huge nucleus was encountered. There was no regular arrangement of the deposits in the cells, and with van Gieson and Mallory stains the tumor was found to contain very little fibrous tissue. Very few blood vessels were found, and those present consisted mostly of spaces lined by a single layer of endothelium and surrounded by abundant fibrous tissue. A few small round cells were scattered here and there.

Sections prepared from frozen material and stained with sudan III showed most of the cells to be filled with fat droplets. These globules were relatively small and appeared as distinct globules in the cells. Careful study led one to the conclusion that the cells which made up the tumor consisted of fat cells in various stages of development, from the stage in which there was no differentiation and the protoplasm appeared granular to the stage of full maturity in which the cells contained numerous droplets of fat.

Sections taken from the polypoid mass showed it to consist of a very loose myxoma-like stroma arranged in a polypoid formation, the external surface being covered by a single layer of epithelium.

Sections of other tumefactions in the breast showed a marked fibrous tissue about ductlike structures in which the fibrous tissue was rather dense and the ducts were lined by cuboidal epithelium.

Sections from other portions of the breast showed what appeared to be a marked increase in the density of the stroma, with a mild round cell infiltration. The ducts in these areas were markedly dilated and were lined with one or two layers of cuboidal epithelium. The lymph glands showed only an inflammatory hyperplasia and no malignant process.

It appears that the breast was the seat of four separate and distinct lesions, namely, pericanalicular fibro-adenoma, intracanalicular fibro-adenoma with marked edema, cystic degeneration and liposarcoma.

DISCUSSION

WILLIAM ANTROPOL: I should like to know whether this case may be considered one of lipoma rather than liposarcoma, and also whether the lipomatous changes in the sections may not be similar to those seen in primary xanthoma (Haagensen,

C. D.: *Am. J. Cancer* **16**:1066, 1932) or in xanthoma secondary to fibro-adenoma, chronic cystic mastitis and other chronic inflammations. The foam cells on the screen resemble those found in these conditions.

PAUL KLEMPERER: The question of embryonal fat cells is difficult. I am inclined to regard as embryonal fat cells polygonal cells which have not one large fat droplet but in which the cytoplasm is honeycombed by the presence of many small fat droplets. This type of fat cell is occasionally found in fat tumors and suggests that one is dealing with an embryonal fat tumor which is called, therefore, a liposarcoma. Two facts have caused me to reconsider the point of view that I have held for a considerable time: I made a study of the embryonal development of fat tissue based on the work of Wassermann in 1926. This author showed that embryonal fat tissue develops from definite mesenchymal foci, which are called primordial fat organs (Toldt). These primordial fat organs consist of reticulated mesenchymal cells which have not yet differentiated to the type of connective tissue cells which are recognized in the mesenchyme in adult life. In fact, the development of the fat tissue begins at about the same time the lymphatic tissue develops from the embryonal mesenchyme. The mesenchymal foci which later develop into lymphatic tissue have exactly the same arrangement and structure as the embryonal primordial fat organs of the human embryo in the fourth month of life. In these stages the fat cell is really an undifferentiated embryonal cell and does not have the appearance of the polygonal cell which has been called the embryonal fat cell. If one studies the fat in lower mammals, one will find that there are two forms of fat present, the white or yellow fat and the brown fat. The brown fat is particularly found in hibernating animals, in which it forms a large glandular mass. It is peculiar that this fat in hibernating animals is composed of polygonal cells. In human beings one finds the same type of polygonal cell, particularly around the thymus region. It is furthermore possible that the ordinary fat cell in a condition of starvation takes on the appearance of the polygonal cell with multiple fat droplets.

In regard to fatty tumors which are composed exclusively of this type of polygonal cells, I have had one case in which I could follow up the patient for many years. The patient, whom I saw nine years ago at the Post-Graduate Hospital, had a tumor which I regarded, because of its histology, as a possible embryonal fat tumor; I suggested that the surgeon watch the patient carefully. I inquired about the patient seven years later when I was studying embryonal fat tumors, and I was told that the patient, who had only a simple excision of the tumor, was in perfect health. This experience, combined with other experiences, has caused me to reconsider the point of view that one should regard these tumors as sarcomas.

In the case reported there were two cells which showed amitotic figures. These figures are also encountered in the type of polygonal fat cell tumor which I should hesitate to regard as a liposarcoma. The question arises, Does a liposarcoma exist at all? Generally malignant tumors which contain fat are found in combination with other embryonal tissue, particularly, as Dr. Lederer has said, with myxomatous tissue. The existence of a liposarcoma, a tumor consisting only of fat cells, is in my opinion questionable. I have seen one tumor which caused me to study the whole question. It was a malignant, recurrent type of tumor which was observed for nine years, and which consisted entirely of embryonal fat tissue in a very early developmental phase. This tumor did not conform with the polygonal fat cell tumor described by Dr. Lederer and Dr. Livingston. There is, furthermore, a theoretical question regarding the designation of a tumor as a sarcoma if it does not consist of connective tissue.

I should like to ask Dr. Lederer why in a case like this a radical operation was performed? Do you recommend the removal of the lymph nodes in the axilla in all cases of sarcoma of the breast?

MAX LEDERER: This case gave us a good deal of cause for study, and the points brought out were fairly well considered. It is probable that we may be accused of a considerable amount of temerity in presenting this case as one of liposarcoma, but we should not have done it without the diagnosis of Dr. Ewing.

who thought that the tumor was a liposarcoma. The lantern slides do not give all the information that is available in this case. As Dr. Klemperer remarked in connection with the previous case, we are at a disadvantage in trying to prove our case by lantern slides, but certain parts of the tumor illustrated by one of the slides consist of compact cells which look sarcomatous and which are undifferentiated. It is not an inflammatory lesion; it is definitely neoplastic. As we studied the sections, we found what we thought might be gradations in the development of the cells from the undifferentiated cell to an adult fat cell, or clear spaces as the fat cells are ordinarily recognized in sections stained with hematoxylin and eosin. Some of the spaces are enormous. The frozen section, which was carefully studied, showed the appearance Dr. Klemperer mentioned, namely, a scattering of fat droplets in the cell bodies. In some instances the cells were packed with these bodies; in others there were only a few, and one could still make out an undifferentiated eosinophilic protoplasm. The tumor bears no resemblance to a xanthoma. That diagnosis was excluded promptly. Furthermore, the amount of inflammation in the breast was very slight; even in the small areas where there occurred cystic disease, there was very little round cell infiltration.

I think that the intracanalicular fibro-adenoma and its cystic appearances were due more to edema than to myxomatous tissue.

We are perhaps adopting a more or less independent attitude in calling the tumor a liposarcoma, but I think that we have just as much reason for calling it that as have those who argue that there is no such thing, because if there can be a fibrosarcoma and a myosarcoma, why cannot there be a liposarcoma? Microscopic study shows that the tumor is malignant; it is not histologically a benign one.

Concerning the radical operation, we have a radical surgeon, Dr. William Linder, at the Jewish Hospital who does not take any chances. He says that rather than expose a patient to a study, which would answer a question of purely academic interest, he would sacrifice the breast. Perhaps he is right. The lymph nodes do not show a malignant process, but he argues that if one waits until they do show definite signs of malignancy, it is too late.

The conclusion concerning this case, especially after fortification by Dr. Ewing's opinion, is that we are dealing with a liposarcoma. It is a most peculiar tumor. There was another nodule in the breast at a distance from the original one which was shelled out. We are thankful for the criticisms or suggestions which may throw light on the specimen. If this case shows further developments, they will be reported.

ALFRED PLAUT: I have seen pseudoxanthomas in my gynecological work at the Woman's Hospital, and I do not think that any pseudoxanthoma I ever saw was like the one under discussion, no matter what kind of inflammation caused it. Guided by accidental findings, I have made for a long time a study of fat giant cells, and I do not think that outside of malignant tumors I have ever seen any fat giant cells like these. A few weeks ago I saw a large liposarcoma of the mesentery which did not contain any other tissues; the resemblance of this tumor to the one demonstrated by Dr. Lederer and Dr. Livingston is very striking. I should have diagnosed this tumor as a liposarcoma without hesitation. If the patient remains well for many years, I should still call the tumor a liposarcoma, and state merely that liposarcomas are clinically benign.

Book Reviews

A Study of Nephritis and Allied Lesions. By John Gray. Medical Research Council, Special Report Series, no. 178. Price, 2s. 6d., net. Pp. 141. London: His Majesty's Stationery Office, 1933.

The book is an excellent example of a recent type of pathologic studies in which a serious attempt is made to correlate gross and microscopic structural changes with the clinical manifestations of disease. It is based on an examination of the kidneys in more than 500 cases and is an analysis of the histologic and clinical findings in all those in which nephritis or an allied type of lesion was evident. This is the second comprehensive study of this subject published by the Medical Research Council, the first being that of Dorothy Russell in 1929 (reviewed in *ARCH. PATH.* 10:344, 1930).

The present monograph is divided into twelve chapters. The introductory chapter states the objects of the investigation, presents a critical discussion of the general principles of classification of nephritis, sets forth the methods employed and describes briefly but adequately the normal and general pathologic histology of the kidney. The succeeding chapters deal with the various types into which the author classifies the disease: acute nephritis, acute focal nephritis, acute nephrosis, subacute and early chronic nephritis, nephrotic nephritis, chronic nephritis, kidney of essential hypertension (arteriolosclerotic kidney) and arteriosclerotic kidney. The last group is considered of little significance as, of itself, the lesion produces no renal clinical phenomena and is characterized by arteriosclerotic focal atrophy. A small group of selected cases is presented with an adequate degree of completeness to illustrate the characteristics of each group.

The main object of this investigation was an attempt to devise a classification of nephritis which would be applicable both clinically and pathologically. The author recognizes the difficulties in framing such a classification. In the first place, two kidneys which are both grossly and microscopically so similar that they must be placed in the same pathologic category may have come from patients who showed fairly marked clinical differences (e. g., in degree of edema). In such cases the clinical data were analyzed with a view to determining whether there existed any underlying unity in spite of the presence of variable factors. In those cases which had some clinical features in common but which showed histologic differences search was made for other clinical features which might serve to distinguish between them. For purposes of classification, sets of clinical features were determined which characterize the different pathologic groups, and agreement between clinical and pathologic groupings was sought partly by attaching special importance to certain clinical features as against others. For example, in distinguishing chronic nephritis from conditions which resemble it in certain respects, such as essential hypertension and nephrotic nephritis, the ability of the kidney to produce a concentrated urine was considered of special importance.

The second difficulty in classification is that of delimiting the various groups from one another, for many of the groupings in any classification of nephritis must represent simply successive phases of the same condition, and inevitably many borderline cases must occur. To overcome this difficulty, descriptions of groups from either the clinical or the pathologic aspect have been composed of a range of possible appearances rather than of a single definite set of appearances. Advantage was taken of all natural clear lines of cleavage, such as are furnished by the first appearance of new features, or the disappearance of earlier ones. This plan was generally found suitable both from the clinical and from the pathologic point of view.

Whether or not the classification of nephritis presented in this monograph gains universal acceptance, it is a contribution to the subject that is worthy of consideration both by pathologists and by clinicians. Clearness in presentation compensates for the absence of illustrations.

Books Received

LYMPHATICS, LYMPH AND TISSUE FLUID. Cecil K. Drinker, B.S., M.D., Professor of Physiology, Harvard School of Public Health, and Madeleine E. Field, A.B., Ph.D., Instructor in Physiology, Harvard School of Public Health. Price, \$3. Pp. 254. Baltimore: Williams & Wilkins Company, 1933.

URINE AND URINALYSIS. Louis Gershenfeld, Ph.M., B.Sc., P.D., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories, Philadelphia College of Pharmacy and Science. Pp. 272, with 36 engravings. Price, limp binding, \$2.75. net. Philadelphia: Lea & Febiger, 1933.

DISEASES OF TRADESMEN. Bernardino Ramazzini (1633-1714). Together with biographical notes translated from the French of Francois Claude Mayer (1928) of Budapest and paragraphs from the preface of Dr. James (1746) of London, and of Dr. James (1922) of New York. The abstracts from the 1746 English Translation of the Ramazzini work emphasize his comments on dermatological disturbances of workmen. Compiled by Herman Goodman, B.S., M.D., New York City. With which is bound Silk Handler's Disease of the Skin, being a study of the clinical aspects, and a recital of the search for the cause including notes on the culture of the silkworm, the handling of the silk from the cocoon to its preparation in the throwing mill for weaving. Herman Goodman, B.S., M.D., New York City. Price, \$1.50. Pp. 95, with 5 figures. New York City: Medical Lay Press, 1933.

CERVICO-VAGINITIS OF GONOCOCCAL ORIGIN IN CHILDREN. Report of a Project of the Bellevue-Yorkville Health Demonstration of New York City. Walter M. Brunet, M.D., Dora M. Tolle, M.D., Sara Alicia Scudder and Anne Ruth Medcalf. Foreword by Emily D. Barringer, M.D., Robert L. Dickinson, M.D., and William H. Park, M.D., Supplement No. 1 of Hospital Social Service Magazine. Price, paper, \$2. Pp. 97, with illustrations. New York, 1933.

ARTERIOSCLEROSIS: A SURVEY OF THE PROBLEM. A Publication of The Josiah Macy, Jr., Foundation. Edited by Edmund V. Cowdry, Washington University, St. Louis. Price, \$5. Pp. 617, with 88 figures. New York: The Macmillan Company, 1933.

EPIDEMIOLOGICAL STUDY OF SCARLET FEVER IN ENGLAND AND WALES SINCE 1900. Hilda M. Woods. Medical Research Council, Special Report Series No. 180. Price, 1s. 3d., net. Pp. 60. London: His Majesty's Stationery Office, 1933.

EXAMENS DE LABORATOIRE DU MÉDECIN PRATICIEN. Guy Laroche, Professor agrégé à la Faculté de Médecine; médecin des hopitaux de Paris. Troisième édition. Price, 50 fr. Pp. 492, with 151 figures. Paris: Masson et Cie, 1933.

A TEXT-BOOK OF NEUROPATHOLOGY. Arthur Weil, M.D., Associate Professor of Neuropathology, Northwestern University Medical School, Chicago. Price, cloth, \$5, net. Pp. 335, with 260 engravings. Philadelphia: Lea & Febiger, 1933.

DIE HISTOPATHOLOGIE DER UTERUSMUCOSA. Ein Leitfaden für Gynäkologen und Pathologen bei der histologischen Diagnostik. Dr. H. T. Deelman, Ord. Prof. der Allgemeinen Pathologie und pathologischen Anatomie der Reichsuniversität Gröningen. Price, paper, 22 marks; bound, 24 marks. Pp. 247, with 248 illustrations. Leipzig: Georg Thieme, 1933.

APPENDICAL OXYURIASIS AND APPENDICITIS

BASED ON A STUDY OF 26,051 APPENDICES

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In a study ¹ of the incidence of oxyurids in 20,969 extirpated appendices completed in 1930, attention was directed to the increasing frequency of appendical oxyuriasis. Since then, histologic examination of 5,082 additional appendices, removed surgically, has revealed oxyurids in 90 instances, an incidence of 311 appendices infested with pinworms in a total of 26,051 (1.19 per cent). In addition to oxyurids, amebas were found in 4 appendices (1 the subject of report ²), *Taenia saginata* in 1 and *Ascaris lumbricoides* in 3. There were no examples of infestation with *Trichuris trichiura*. In view of the increasing incidence of appendical oxyuriasis, its etiologic relationship to appendicitis becomes a matter of interest and importance.

REVIEW OF THE LITERATURE

While appendical helminthiasis had been described many years before, Still and Metchnikoff must be given chief credit for arousing interest in the condition. Still ³ found a high incidence of oxyuriasis in children at autopsy. He noted certain differences in the gross between the appendices containing oxyurids and those showing acute inflammation. In the former type there were always injection of the serosa, thickening of the wall and chronic catarrh. Metchnikoff ⁴ directed attention to a possible relationship between appendicitis and intestinal parasitism, although he was concerned with trichuriasis rather than with infestation with oxyurids. Rheindorf ⁵ has been a staunch and vigorous proponent of the theory of a causal relationship between oxyuriasis and appendi-

From the Department of Pathology, University of Michigan; C. V. Weller, Director.

1. Gordon, H.: *Ann. Int. Med.* **4**:1521, 1931.
2. Harrison, W. F.: *Ann. Int. Med.* **2**:1081, 1929.
3. Still, G. F.: *Brit. M. J.* **1**:898, 1899.
4. Metchnikoff, L.: *J. d. praticiens* **15**:185, 1901.
5. Rheindorf, A.: (a) *Berl. klin. Wchnschr.* **49**:451 and 503, 1912; (b) *Med. Klin.* **9**:53, 96, 133 and 177, 1913; (c) *Frankfurt. Ztschr. f. Path.* **14**:212, 1913; (d) *Med. Klin.* **9**:623, 1913; (e) *Berl. klin. Wchnschr.* **51**:1211 and 1271, 1914; (f) *Centralbl. f. Bakt.* **74**:604, 1914; (g) *Die Wurmfortsatzentzündung*, Berlin, S. Karger, 1920.

citis. His arguments, as well as the opposite views of Aschoff⁶ and his pupils, Hueck⁷ and Brauch,⁸ are discussed in detail in a later section.

Hippius and Lewinson⁹ believed that oxyurids are capable of causing traumatic injuries to the mucosa of the appendix, thus producing a favorable portal for the entrance and multiplication of pathogenic microorganisms. Wagener¹⁰ concurred in this view. Riff,¹¹ favoring the thesis of a positive causal relationship, adduced the further arguments that oxyuriasis and appendicitis are most frequent between the ages of 5 and 20, that neither oxyuriasis nor appendicitis occurs before the twenty-first day of postnatal life, and that there is some evidence that appendicitis is a familial and a contagious disease. Fischer¹² used somewhat similar arguments to advance a negative view. He pointed out that appendicitis is relatively rare and oxyuriasis comparatively frequent before the tenth year. He stressed the finding of oxyurids in only 5 of 51 inflamed appendixes as against their presence in 29 of 105 and 32 of 39 normal appendixes. Finally, he drew attention to the reputed rarity of appendicitis in the native Chinese despite the extraordinary frequency of oxyuriasis among Orientals.

Drigalski and Koch¹³ found the same percentage of oxyuriasis in 100 children from whom the appendixes had been removed and in 100 control subjects of similar age groups. Schröpl,¹⁴ prompted by the observation of certain nervous manifestations in patients harboring oxyurids, tested the toxicity of the parasites by injecting an alcoholic extract of their bodies. He noted an increased reaction of sensitization of the skin, and he believed that the parasites are capable of provoking an immediate local, as well as a systemic, effect. Ragaine¹⁵ and Garin¹⁶ supported the view that intestinal parasites frequently may cause inflammation in the appendix. Garin emphasized especially the capacity of the oxyurids for inoculating the appendix with pathogenic microorganisms. MacLean¹⁷ found enormous numbers of parasites in the appendixes of Chinese at autopsy, without any important sign of inflammation. He concluded that while oxyurids are capable of penetrating

6. Aschoff, Ludwig: (a) *Die Wurmfortsatzentzündung*, Jena, Gustav Fischer, 1908; (b) *Ergebn. d. inn. Med. u. Kinderh.* **9**:1, 1912; (c) *Med. Klin.* **9**:249, 1913; (d) *Berl. klin. Wchnschr.* **51**:1504, 1914; (e) *ibid.* **57**:1041, 1920.

7. Hueck, O.: *Frankfurt. Ztschr. f. Path.* **13**:434, 1913.

8. Brauch, M.: *Beitr. z. path. Anat. u. z. allg. Path.* **71**:207, 1923.

9. Hippius, A., and Lewinson, J.: *Deutsche med. Wchnschr.* **33**:1780, 1907.

10. Wagener, O.: *Virchows Arch. f. path. Anat.* **182**:145, 1905.

11. Riff, A.: *Presse méd.* **27**:521, 1919.

12. Fischer, W.: *Deutsche Ztschr. f. Chir.* **183**:222, 1923.

13. Drigalski, W., and Koch, E. W.: *Deutsche med. Wchnschr.* **51**:309, 1925.

14. Schröpl, E.: *Deutsche med. Wchnschr.* **52**:1508, 1926.

15. Ragaine, Paul: *L'appendicite vermineuse*, Thèse de Paris, 1905, no. 85: quoted by Hueck.⁷

16. Garin, C.: *Gaz. d. hôp.* **83**:1455, 1910.

17. MacLean: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **21**:36, 1909.

beneath the mucosa, they cannot be considered seriously as factors in the causation of appendicitis.

Eastwood¹⁸ examined both surgical and autopsy specimens and found pinworms in about the same proportion in each group. He found no evidence suggesting that the parasites are a frequent cause of appendicitis. Ney¹⁹ distinguished three classes of infestation of the appendix with pinworms: a group showing worms, but without symptoms, common in children; a group grossly negative, but with microscopic inflammatory foci, and a group with gross and microscopic evidences of inflammation, which may progress to gangrene. His microscopic description, however, was neither detailed nor convincing. Harris and Browne²⁰ believed that the parasites are capable of provoking a morbid response because of the presence of degenerative and exudative changes about them with the destruction of tissue in their wake. However, they admitted that "those appendixes demonstrating positive worms in the gross could not be differentiated through the histopathologic study from those which were negative for the nematodes."

Innes and Campbell²¹ found infestation with oxyurids much less frequently in normal than in inflamed appendixes. They supported the theory of a clinical type of appendicitis caused by oxyurids, but could find no relationship between suppurative appendicitis and infestation with nematodes. Cecil and Bulkley²² grouped their material in four divisions:

1. Appendixes containing oxyurids as a coincidence. These showed only mild catarrh and lymphoid hyperplasia.
2. Appendixes showing penetration of the mucosa with punctate hemorrhages but without inflammatory reaction.
3. Appendixes in which oxyurids were present and producing destructive, ulcerous lesions in the mucosa.
4. Gangrenous appendixes showing occurrence of oxyurids; the relationship, however, is a matter of some uncertainty.

They stressed the presence of mild catarrh and lymphoid hyperplasia as almost constant accompaniments of oxyuriasis. To them, these changes constituted important signs of reaction, since they were present in a control group of appendixes obtained at autopsy and containing worms, as well as in those removed at operation. However, the very fact that they were present in the control group and likewise in many appendixes not containing worms argues that these changes can be provoked by causes other than parasites. Cecil and Bulkley explained the paucity of inflammatory changes on the basis of a negative chemotaxis, but also stressed the fact that it is practically impos-

18. Eastwood, E. H.: *J. Path. & Bact.* **26**:69, 1923.

19. Ney, G. C.: *Bull. Johns Hopkins Hosp.* **23**:123, 1912.

20. Harris, W. H., and Browne, D. C.: *J. A. M. A.* **84**:650, 1925.

21. Innes, J. A., and Campbell, A. E.: *Parasitology* **7**:189, 1914.

22. Cecil, R. L., and Bulkley, K.: *J. Exper. Med.* **15**:225, 1912.

sible to make complete serial sections of the appendix, so that very minute hemorrhages may be missed.

Suzuki ²³ compared operative and postmortem appendixes, and noted hemorrhages in the former, but none in the latter group when the parasites occurred in the appendical wall. He related this difference to the motility of the parasites in the surgical specimens, and to their quiescence in the necropsy material. He proposed the term "appendicopathia oxyurica traumatica" for appendixes showing this change. Suzuki ²³ classified the extirpated appendixes in three groups. The first two correspond essentially to the first two groups of Cecil and Bulkley,²² except for the suggested nomenclature "appendicopathia oxyurica traumatica." A third group, of which he found but a single example, he termed "appendicitis oxyurica" because of an essential causal relationship between the parasites and the inflammation. Aschoff,^{6c} Hueck ⁷ and Brauch ⁸ also believed that the worms are capable of provoking painful muscular spasms in the appendix.

Ssolowjew ²⁴ found shallow half moon-shaped depressions in the mucosa accompanied by karyolysis, pressure atrophy and local eosinophilia. He believed that these changes favored secondary bacterial invasion, thus ascribing an indirect rôle to the parasites. Such a relationship, however, was not subject to histologic verification in every instance. Steichele ²⁵ concluded that true appendicitis cannot be distinguished clinically from the painful syndrome evoked by the parasites. Jaroschka ²⁶ expressed a similar view. He believed that the oxyurids are capable of causing local damage to the wall of the appendix, either by mechanical pressure or by toxic action, these changes being accompanied by pain. True appendicitis, however, occurred only rarely in association with the worms.

In addition to the more elaborate studies cited, the literature abounds with brief clinical reports. Nicolaus ²⁷ reported five examples of appendical oxyuriasis. He found threadworms in the wall of the organ and offered evidence in support of the claim that the penetration had taken place as a preoperative, vital phenomenon. Ehlers ²⁸ described an instance of appendicitis of acute onset. The appendix contained numerous pinworms and showed mucosal defects differing from those produced by "paraffin impregnation." He noted acute periappendicitis, and ascribed this to fecal absorption. Rheindorf ^{5b} drew attention to identical changes. Wood ²⁹ reported a group of seven appendixes removed at operation, all containing oxyurids. He described symptoms differing clinically from those usually associated with appendicitis.

23. Suzuki, K.: Surg., Gynec. & Obst. **21**:702, 1915.

24. Ssolowjew, N. J.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **41**:20, 1928.

25. Steichele, H.: Arch. f. klin. Chir. **135**:373, 1925.

26. Jaroschka, K.: Deutsche Ztschr. f. Chir. **183**:99, 1923.

27. Nicolaus, H.: Deutsche Ztschr. f. Chir. **215**:133, 1929.

28. Ehlers, H. W. E.: Deutsche Ztschr. f. Chir. **213**:275 1929.

29. Wood, W. A.: M. J. Australia **1**:234, 1918.

Garlough³⁰ noted acute or subacute inflammatory changes, many polymorphonuclear leukocytes and from a few to many eosinophils in appendixes containing pinworms. Bloom³¹ found pinworms of minor importance in his series. The individual case reports presented by Wakefield,³² Culhane,³³ Rogers,³⁴ Lediard³⁵ and Ashhurst³⁶ offer data insufficient for a well considered opinion.

In summary, it may be said of the literature that much of it is only too evidently founded on conviction instead of on objective data. Some of the authors have been forced to bolster their theses by arguments based on analogy, and the conscientious reader is more apt to be confused than helped by the mass of evidence available.

MATERIAL AND METHODS

My material consisted of 26,051 appendixes received for routine diagnosis at the pathologic laboratories of the University of Michigan during the period from July 1, 1894, to Oct. 31, 1932. Only surgical specimens were included in this group. For reasons to appear later, autopsy specimens were not considered necessary for control purposes. Most of the appendixes came from residents of Michigan, and were removed in the University Hospital and in other hospitals distributed over the state.

The appendixes were received in 10 per cent formaldehyde. Since the beginning of 1903, blocks for impregnation with paraffin have been taken as a routine measure to include representative portions of the proximal, mesial and distal thirds, while prior to that period the organs were sectioned at but one or two levels. When indicated, blocks have been taken from four or more levels. Duplicate sections were usually prepared, but serial sections were not attempted since the technical procedure was purely routine. In the course of the present study many of the old blocks have been resectioned. With few exceptions, the diagnoses for the entire series have been rendered by the directors of the laboratories, Dr. A. S. Warthin and Dr. C. V. Weller.

In conducting this study, the following outline was followed:

1. Anatomic distribution of the parasites and the incidence of such distribution
2. Pathologic changes
 - (A) The lesions
 - (a) Incidence
 - (b) Description
 - (c) Incidence of catarrhal reaction
 - (B) Response of the lymphoid tissue
 - (C) Local eosinophilia
3. Clinical significance
4. Conclusions

30. Garlough, L. N.: J. A. M. A. **80**:422, 1923.

31. Bloom, C. J.: New Orleans M. & S. J. **81**:377, 1928.

32. Wakefield, R. W.: J. A. M. A. **50**:1904, 1908.

33. Culhane, T. H.: J. A. M. A. **54**:48, 1910.

34. Rogers, L.: New York M. J. **118**:620, 1923.

35. Lediard, H. A.: Edinburgh M. J. **32**:762, 1925.

36. Ashhurst, A. P. C.: Am. J. M. Sc. **138**:583, 1909.

RESULTS

ANATOMIC DISTRIBUTION OF THE PARASITES

In table 1 is shown the anatomic relationship of the parasites to the structure of the appendix. The parasites were present in the lumen alone in 256 instances (82.31 per cent). In 22 additional appendixes, however, while oxyurids were present in the lumen, they were more intimately related to the mucosa. In this group the mucosa showed shallow half moon-shaped depressions approximately corresponding in size and in shape to the worms. Of the remaining 33 appendixes, 17 had pinworms both in the submucosa and in the lymphoid follicles, 12 contained them in the submucosa alone, and 4, in the lymphoid follicles only.

TABLE 1.—*Anatomic Relationship of the Oxyurids to the Structure of the Appendix*

Location of Oxyurids	Cases	Percentage
In the lumen (not attached to mucosa).....	256	82.31
In the lumen (attached to mucosa).....	22	7.07
In the submucosa and in the lymphoid follicles.....	17	5.47
In the submucosa only	12	3.86
In the lymphoid follicles only.....	4	1.29
Total.....	311	

These figures are in general agreement with the findings of other investigators. Rheindorf ^{5a, b, c} has persistently reported a much higher incidence of penetration. This, he claimed, may not be apparent unless serial sections are prepared, and the entire appendix is sectioned.

PATHOLOGIC CHANGES IN APPENDICAL OXYURIASIS

The Lesions.—Incidence and Description: In 12 of the 22 appendixes containing oxyurids in intimate relationship to the mucosa, there were lesions peculiar to the parasites and unquestionably related to them. In 6 the lesions could not with certainty be ascribed to the worms, while in the remaining 4 no characteristic lesions could be demonstrated. The lesions ascribed to the worms varied in degree and in extent, so that an uninterrupted series could be built up from small half moon-shaped depressions to actual, although shallow, erosions (figs. 1 and 2). In some instances the defects represented simply the results of pressure. My material shows that pressure effects occur particularly when worms are caught between a fecal concretion and the mucosa. This relationship may escape recognition if the concretion has been dislodged in the sectioning of the appendix. When local defects corresponding to the position of the worms are associated with dilatation of the lumen and general atrophy of the mucosa, the effect of such calculi can be deduced. These lesions may show flattening of an epi-

thelium which is still smooth and intact, and are characterized only by a locally increased production of mucin. In a lesion of more marked degree there is an approach to true ulceration. These erosions have certain peculiarities by which they may be recognized. They are small



Fig. 1.—Small pressure lesion in the mucosa, showing the oxyurid responsible for the lesion. Note the fine membrane adherent to the parasite. Hemalum and eosin stain; $\times 100$.

and lie in close relationship to the causal worms; minute punctate hemorrhages may be nearby, and along the free surface of each erosion may be seen a fine membrane composed of desquamated epithelial cells, mucin and lymphocytes. Part of the membrane may be adherent, also, to the worm (fig. 1).

In contrast to the lesions described, some appendixes contain mucosal defects without any evidence of tissue reaction or hemorrhage. A defect of the latter type is shown in figures 3, 4 and 5, which represent different levels cut from the same block of tissue. Such appendixes are smooth-walled, and there is no trace of hemorrhage or of an alternative, defensive or protective reaction. In the submucosa and the lymphoid tissue of the appendixes containing oxyurids are changes analogous to the second type of mucosal defects. In this group the worms lie in

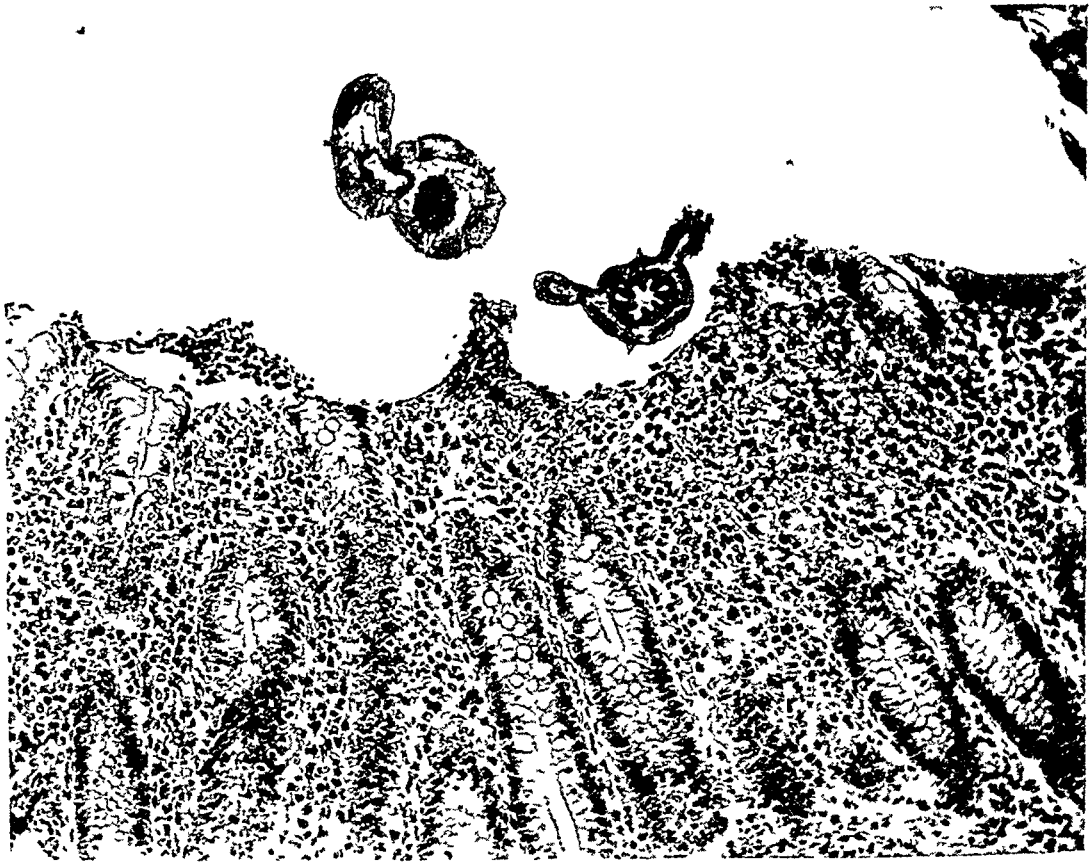


Fig. 2—Two small mucosal erosions with the causal oxyurids. Hemalum and eosin stain; $\times 75$.

smooth-walled defects without any evidence of reaction or of hemorrhage, although the winding channels made by the migrating worms are evident (figs. 4 and 5).

The two types of defects described, which are known to be produced by the worms, must be differentiated from technical artefacts. One of the most common of these artefacts is a large gaping space between the mucosa and the musculature. This artefact, produced by surgical trauma, occurs with equal frequency in appendixes containing oxyurids and in those free from them. Sometimes the oxyurids are found in

large numbers in such spaces, and individual worms may be found embedded in the tissue débris (fig. 6). Attention is directed to such defects to emphasize the fact that the oxyurids play no part in their production.

The lesions described have aroused considerable controversy. Rheindorf^{5a, b, c} failed to distinguish between the first two types of defects.

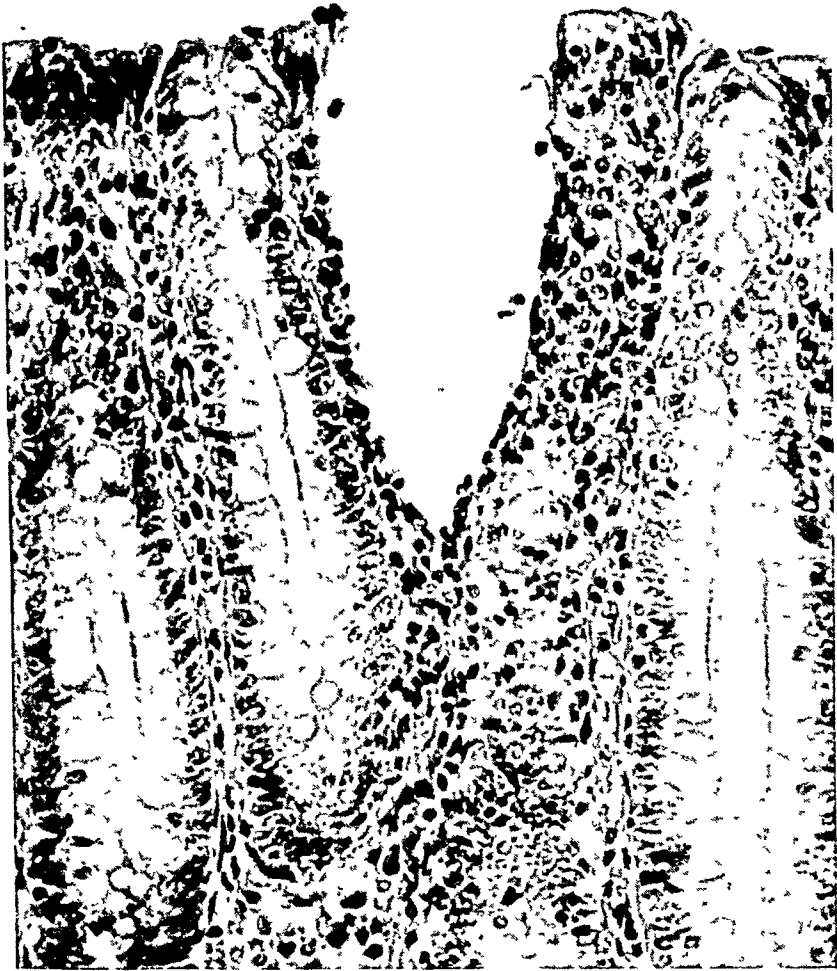


Fig. 3—Mucosal defect with characteristic smooth walls and without hemorrhage or tissue reaction. The portal of entry for postoperative migration. Hemalum and eosin stain; $\times 100$.

He warned against the dangers of secondary bacterial invasion when the defects are present. He believed that penetration into the submucosa and the lymphoid tissue is a common phenomenon. If this were true, one would expect the ingestion of blood by the worms, but in my material only an occasional parasite was seen with red blood cells in its intestinal tract. This finding is sufficiently rare to make it unlikely that oxyurids are thereby responsible for undernutrition, as has been claimed

by Rheindorf.^{5d} Garin¹⁶ suggested that the parasites are able to digest the epithelium of the appendix, but I found no evidence of this. Harris and Browne²⁰ and Cecil and Bulkley²² also reported oxyurids in the wall of the appendix, and described small hemorrhages and necrotic lesions at the site of penetration. Aschoff,^{6c, d} Hueck⁷ and Brauch,⁸



Fig. 4.—The winding channel leading from the mucosal defect seen in figure 3. The causal worm is in the submucosa. Hemalum and eosin stain; $\times 100$.

on the contrary, insisted that both the small mucosal lesions and the larger defects are artefacts, in part due to operative trauma, and in part to impregnation with paraffin. Brauch claimed that impregnation with paraffin is always accompanied by artefacts, with more or less injury to the mucosa. Aschoff,^{6c} however, modified his earlier stand^{6a} as to the frequency and significance of appendical oxyuriasis. At first he

dismissed oxyuriasis as of consequence to the host, but later admitted the ability of oxyurids to penetrate the tissues. He noted the characteristic smooth-walled defects and the winding passages without reaction or hemorrhage. For this group he^{6c} suggested the term "appendicopathia oxyurica," having in mind the production of pain and yet the

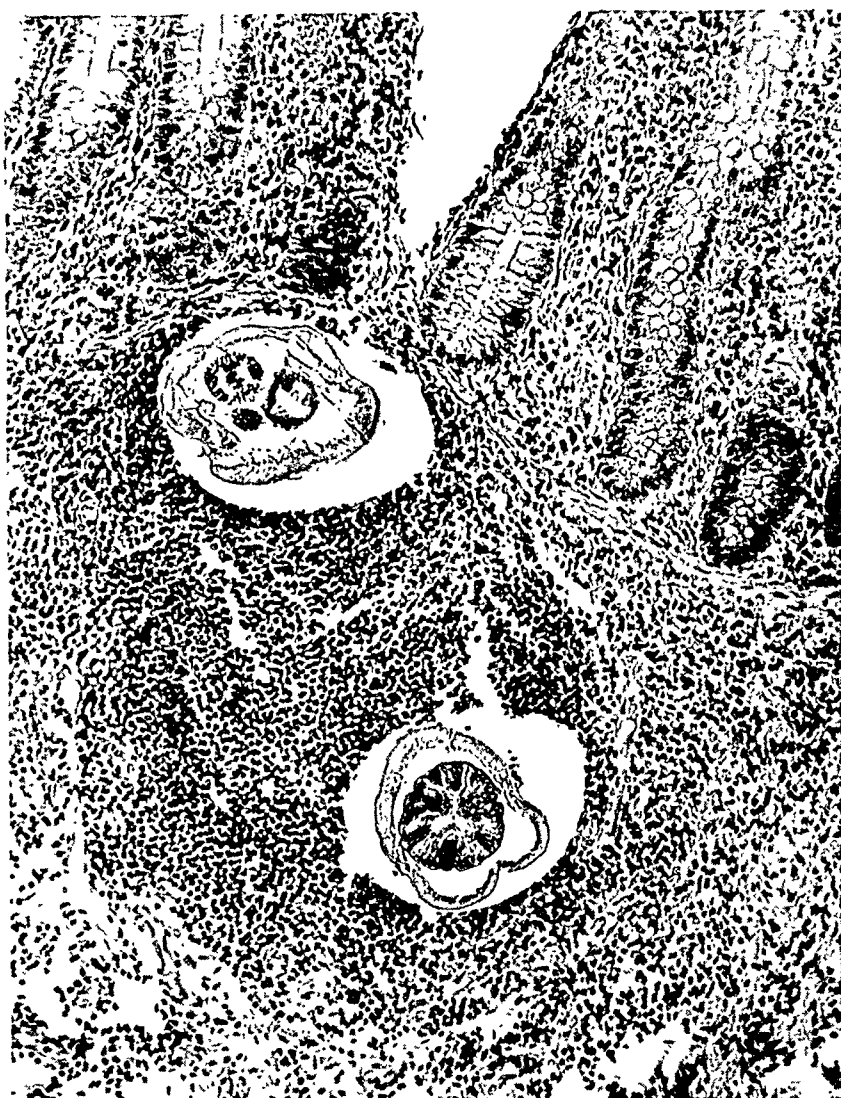


Fig. 5.—The channel seen in figure 4 leads into a lymphoid follicle with an oxyurid in situ. The passage and defect are smooth-walled, and there is no hemorrhage or inflammation. Postoperative migration. Hemalum and eosin stain; $\times 75$.

absence of inflammation. Suzuki²³ considered some, but not all, of the defects described by Rheindorf as of the nature of artefacts. Contrary to Aschoff, he found small traumatic hemorrhages about the passages made by the worms. These hemorrhages were present in appendixes removed at operation and absent in appendixes removed post mortem.

He explained the difference on the basis of reduced motility of the worms in the latter, and suggested the term "appendicopathia oxyurica traumatica" for the condition as found associated with hemorrhages.

A more satisfactory explanation than any found in the literature offers itself to account for the defects of the second type in my description, namely, the presence of oxyurids in the appendical wall. Since none of my sections showed hemorrhage or reaction about the worms in the lymphoid tissue of the submucosa, I am forced to conclude that

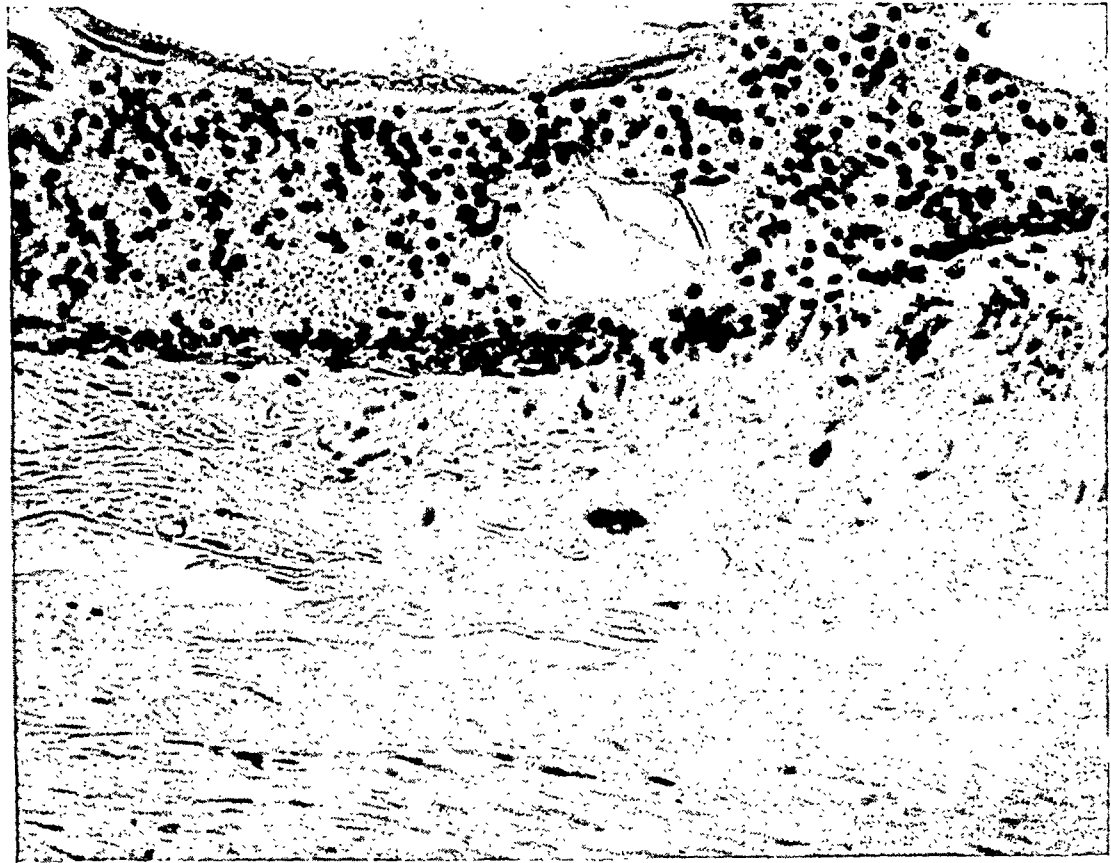


Fig. 6.—Oxyurids at the site of an artefact due to operative trauma. To the left of the lower worm there is a small amount of fecal debris. Note the nuclear clumping in the submucosa and the absence of inflammation. Hemalum and eosin stain; $\times 100$.

penetration occurred subsequent to operation. Only this theory of post-operative migration explains all of the observations of previous investigators as well as mine. Not only does it explain the otherwise insurmountable difficulty of complete lack of hemorrhage, but it also makes clear why no one has ever proved the production of inflammation by the carrying of bacteria from the appendical lumen into the tissues in or on the bodies of the worms. Likewise it explains the paucity of

observations of encysted worms or of foreign body reaction about necrotic worms in the appendical wall, my large material affording but a single doubtful example of this. The presence of the winding channels rules out artificial implantation. This postoperative, or at times postmortem, migration probably finds its explanation in the attempts of the worms to escape from a changing environment as the appendix cools, its p_H changes or the fixing fluid begins to penetrate into its interior. (Experimental investigation of the soundness of this theory is now being undertaken.) If it is physically possible for the worms to migrate into the tissues after operation, the possibility remains that they may do so before operation, but no example of this was found in my material. If such preoperative migration ever occurs, it must be exceedingly rare.

Incidence of Catarrhal Reaction: Still³ first suggested a special type of catarrhal response to invasion of the appendix by oxyurids. Many writers have corroborated this finding. In my series the degree

TABLE 2.—*Degree of Catarrh in Relation to Oxyurids*

Degree	Appendixes Containing Oxyurids	Control Group
0	14 (4.5%)	6 (4%)
±	104 (33.4%)	54 (36%)
+	104 (33.4%)	56 (37.3%)
++	89 (28.6%)	34 (22.6%)

of catarrh was evaluated on the basis of the amount of mucin and the number of goblet cells. The results are expressed in four grades of severity (table 2). Only for the group graded ++ is the term "catarrhal appendicitis" applicable. A control group of 150 appendixes removed surgically from patients of similar age and sex as those from whom the oxyurid-containing appendixes came was studied with the same criteria in mind. As appears in the table, the results do not lend support to the concept of a catarrhal type of appendicitis caused by oxyurids. Appendical catarrh is dependent on general as well as on local conditions in which the oxyurids do not necessarily play an important part.

Response of the Lymphoid Tissue.—Lymphoid hyperplasia as a response to appendical oxyuriasis has been described by many writers (Rheindorf,^{5c, e} Jaroschka,²⁶ Cecil and Bulkley,²² Wood²⁹ and others). Jaroschka suggested that the lymphoid hyperplasia is an expression of the toxic effect of the worms. In assessing the degree of lymphoid hyperplasia in my material (table 3), attention was directed to the size and the number of follicles and to the appearance of the germ centers. The control group previously used was similarly evaluated. My find-

ings do not substantiate the claim that appendical oxyuriasis is attended by lymphoid hyperplasia of an unusual degree. Instead, the special degree of constitutional lymphatism is probably a much more important factor. If the host belongs to the thymicolymphatic constitutional group, the lymphoid tissue of the appendix shares in the generalized lymphoid hyperplasia characteristic of this constitution. The age of the host also is important. Other things being equal, the lymphoid tissues of children are functionally more active and anatomically larger than those of adults. Since oxyuriasis is particularly a disease of childhood, comparative series must be balanced as to age. Certainly Rheindorf's contention of lymphoid hyperplasia in a peculiar association with oxyuriasis, so marked as to lead to stasis in the appendix, cannot be substantiated. When such a degree of hyperplasia is present, it would

TABLE 3.—*Effects of Oxyurids on the Lymphoid Apparatus*

Observation	Oxyurids Present	Control Group
Follicles normal.....	149 (47.91%)	67 (44.6%)
Follicles atrophic.....	45 (14.47%)	24 (16%)
Follicles hyperplastic		
Slight.....	60 (19.29%)	23 (15.3%)
Marked.....	57 (18.32%)	36 (24%)

TABLE 4.—*Local Eosinophilic Response to Oxyurids*

Increase in Eosinophils	Oxyurids Present	Control Group
None.....	187 (60.12%)	82 (54.6%)
Slight.....	108 (34.73%)	58 (38.6%)
Marked.....	16 (5.14%)	10 (6.6%)

seem more reasonable to relate it to the constitutional make-up of the host. The studies of Drigalski and Koch,¹³ who found a relatively high incidence of oxyuriasis in children of asthenic habitus, lend support to the constitutional concept, since the thymicolymphatic and asthenic constitutions are frequently associated.

Local Eosinophilia.—Several authors have investigated the degree of local eosinophilia accompanying appendical oxyuriasis, with varying results. My findings are summarized in table 4. The degree of eosinophilia was graded according to the average number of eosinophils in typical low power fields and according to the extent (depth) of infiltration. Comparison of the infested and control groups shows that local eosinophilia is not significantly increased on invasion with oxyurids. As with lymphoid hyperplasia and catarrh, so with local eosinophilia, the response is probably dependent on local and general factors and

independent of the parasites. While no certain relationship appears in this material between the degree of lymphoid hyperplasia and local eosinophilia, there is evidence to show that both are conditioned by the constitutional make-up of the host (Pende³⁷ and Macdonald³⁸). Appendical eosinophilia is also in part dependent on the chronicity of the inflammation.

CLINICAL SIGNIFICANCE

While the frequency of oxyuriasis as reported for North America lags far behind the figures submitted from many of the European centers, the increasing incidence of infestation merits analysis in regard to its possible clinical import. A majority of the authors cited are agreed that oxyuriasis is of significance to the host. As mentioned, Aschoff^{6c} suggested the term "appendicopathia oxyurica" for the painful morbid condition thought to be caused by oxyurids in some appendixes. He admitted penetration of the tissues by the worms, but denied that the mucosal defects are other than artefacts. Along with Hueck,⁷ Brauch⁸ and others, he made much of the fact that "appendicopathia oxyuria" is not accompanied by a high temperature. Rheindorf,^{5b} on the other hand, noted a moderately high fever in some of his patients. Many surgeons, however, do not regard the fever as of value for the early diagnosis of appendicitis. Coller³⁹ expressed the belief that waiting for fever as a sign of acute appendicitis is dangerous. Aschoff^{6a} and Hueck⁷ suggested that the differentiation between true (primary) appendicitis and the pseudo-appendicitis of oxyuriasis is important, since the latter lends itself to correction by means of vermifuges and is not relieved by operation. Oppe⁴⁰ warned against the use of vermifuges, which call for purgation. Wood²⁹ noted certain differences between appendical oxyuriasis and appendicitis—a history of intermittent illness over a long period, absence of vomiting, slight leukocytosis, fever and "reflex nervous symptoms out of all proportion to the severity of the local lesion" being present in the former. He did not favor the use of anthelmintics.

With regard to the fibrosis so commonly seen in appendixes containing oxyurids, Rheindorf^{5c} related the increase in connective tissue to the presence of the parasites. In favor of this view he cited the higher incidence of oxyuriasis in children over 6 years of age, compared with younger children. He suggested that the oxyurids may disappear after

37. Pende, N.: *Constitutional Inadequacies*, Philadelphia, Lea & Febiger, 1928.

38. Macdonald, I. G.: *Ann. Int. Med.* **6**:253, 1932.

39. Coller, F. A.: Personal communication to the author.

40. Oppe, W.: *München. med. Wchnschr.* **50**:859, 1903.

first causing mucosal lesions, and that the lesions gradually heal with the formation of scar tissue. This, in turn, favors kinking of the appendix, leading to severe appendicitis as a remote consequence of the infestation. Aschoff^{6a, b} and Hueck⁷ denied that oxyurids cause a sclerosing type of appendicitis, directly or indirectly. They considered the fibrosis a senile or an involutionary change.

The material under review does not lend itself to detailed clinical analysis. In table 5 are presented the pathologic diagnoses of the conditions in appendixes containing oxyurids. This table differs from a similar one appearing in a previous publication.¹ The latter showed the percentage occurrence of oxyuriasis for all the appendixes. The present table refers only to the 311 appendixes containing oxyurids. In none of the 71 appendixes showing active inflammation could the inflammation be attributed to the parasites. This claim is based on the fact that in these the worms were present only in the lumen, with no evidence of mucosal

TABLE 5.—*Pathologic Diagnoses Made on Appendixes Containing Oxyurids*

Diagnosis	Total	Percentage	Relationship to Oxyurids
Old recurrent appendicitis (no recent inflammation)	191	61.41	0
Active recurrent appendicitis.....	57	18.32	0
Recurrent, obliterating appendicitis.....	31	9.97	0
Active periappendicitis	18	5.78	0
Acute suppurative appendicitis.....	8	2.57	0
Acute purulent appendicitis.....	4	1.28	0
Acute gangrenous appendicitis.....	2	0.64	0

involvement. In no instance was there any sign of a more severe or advanced degree of inflammation at levels containing the worms than at levels free from parasites. Less direct evidence can be adduced by a statistical comparison of the appendixes without worms and those infested with oxyurids. Of the former, 26.37 per cent showed severe inflammation; of the latter, 22.85 per cent. Correction of the general operative group for age to correspond with the restricted age group favored by infestation with oxyurids yields a much higher incidence of severe inflammation (42.35 per cent). In the wall of an appendix the lumen of which contained oxyurids there was seen a granulomatous area made up of concentrically arranged fibroblasts and a few foreign body giant cells (fig. 7). The central portion of this granuloma contained a large oval calcified mass. Additional sections from the same block failed to show further trace of the area. While proof of its nature is not at hand, the possibility remains that it may have represented a dead oxyurid. The remainder of the appendixes containing oxyurids showed only old fibrosis with no evidence of recent inflamma-

tion, changes entirely comparable to those found in many appendixes without worms.

The term "appendicopathia oxyurica" possesses sufficient merit to warrant its retention, but it should be applied only when the appendix

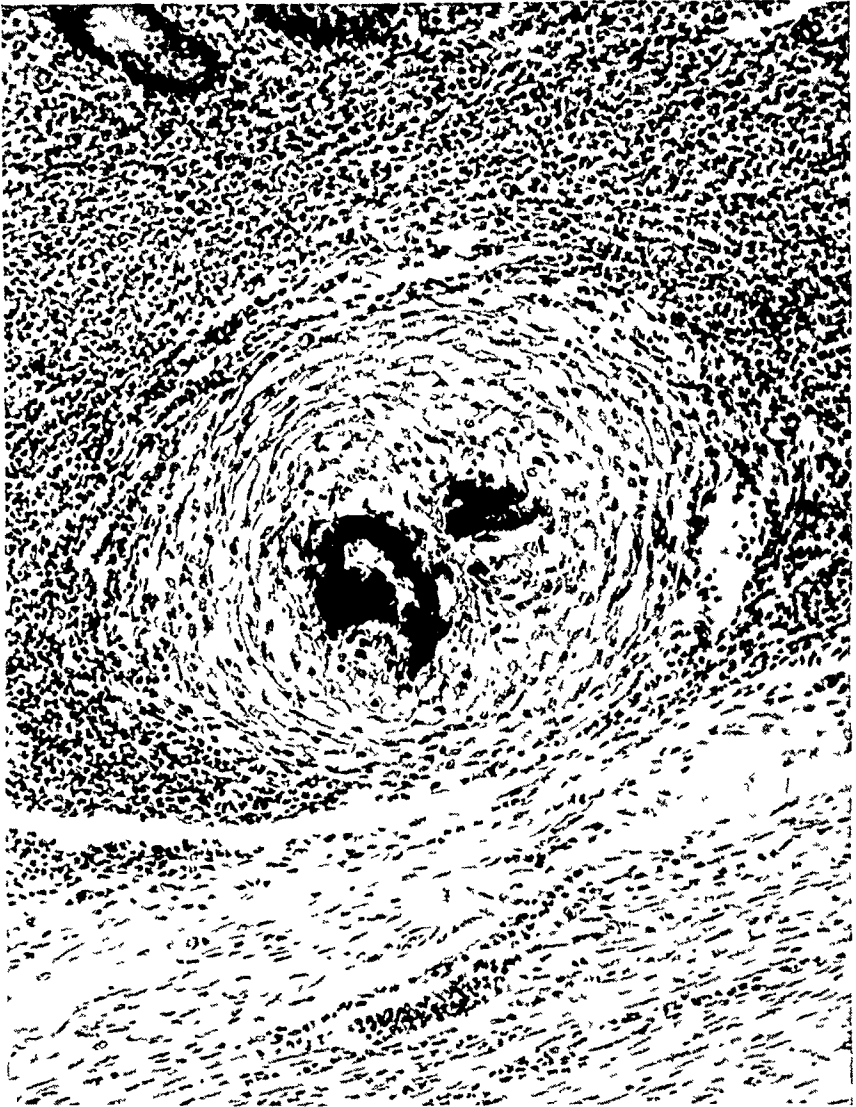


Fig. 7.—Foreign body pseudotubercle containing oval mass of calcified material, with well marked fibroblastic reaction and a few giant cells about the foreign body. An unproved but probably encysted necrotic oxyurid. Hemalum and eosin stain; $\times 75$.

shows evidences of intravital erosion or invasion. The mere presence of oxyurids in the walls of the appendix is not proof of etiologic significance. My material supports the view that oxyurids are not a significant cause of appendical pathologic changes.

CONCLUSIONS

1. The incidence of appendical oxyuriasis is increasing. Oxyurids were found in 311 of 26,051 (1.19 per cent) appendixes removed at operation. In the first 20,969 appendixes in this series, the incidence was 1.04 per cent.

2. Oxyurids occasionally cause minute mucosal lesions in the appendix. These lesions are accompanied by evidence of living tissue reaction: punctate hemorrhages, slight exudation and necrosis. The lesions occurred in 12 instances only; to this condition the term "appendicopathia oxyurica" may properly be applied.

3. In 256 instances the parasites occurred in the lumen of the appendix without producing visible lesions.

4. In 33 instances oxyurids were found in the wall of the appendix. Evidence is adduced to show that in this group penetration occurred after operation in every instance. This type of invasion is therefore of no pathologic or clinical significance.

5. No examples of appendicitis oxyurica occurred in my material.

6. Oxyuris vermicularis is not a significant cause of appendical pathologic changes.

SPONDYLITIS OF SWINE ASSOCIATED WITH BACTERIA OF THE BRUCELLA GROUP

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The widespread distribution of bacteria of the Brucella group among goats, cattle and swine, the not infrequent occurrence of undulant fever among human beings and the etiologic relationship of this disease to Brucella infections of animals constitute a public health problem of significance. The source of infection of undulant fever of man is often obscure, although there has been a popular tendency to incriminate the milk supply in many instances in which acceptable proof of the infectiousness of the milk was not presented. It is important, therefore, to keep in mind possible sources of infection other than that of milk.

In the last twelve months we have had an opportunity to study a spontaneous disease of swine characterized by the occurrence of spondylitis. From many of the lesions we isolated an organism of the Brucella group, which proved to be definitely pathogenic for certain laboratory animals.

SOURCE OF MATERIAL STUDIED

Our material, which consisted of specimens from twenty-four swine, was obtained from abattoirs under the supervision of the Division of Meat Inspection of the Bureau of Animal Industry of the United States Department of Agriculture. Although the exact locality from which the respective swine originated is not known, the majority of the animals from which lesions were obtained were raised in Iowa and Minnesota.

All the animals were subjected to competent antemortem inspection after their arrival at the respective abattoirs, and none manifested physical signs to suggest the presence of lesions found subsequent to slaughter. In fact, with the exception of an animal which before slaughter was observed to be affected with the granulomatous condition known as "scirrhus cord," all the swine were apparently normal and healthy, differing in no respect from the thousands of others slaughtered in the same period and found at necropsy to be without gross evidence of disease.

From the Institute of Experimental Medicine, the Mayo Clinic.

INCIDENCE

The condition which we have designated as spondylitis is by no means prevalent. Although it is not uncommonly seen in abattoirs in which large numbers of hogs are slaughtered daily, it is observed in only a small percentage of the total number of carcasses examined. We have little information concerning the incidence of the condition, but we have been able to secure some data that perhaps are of significance. Eleven of the specimens studied were obtained from one abattoir during a period when 67,000 swine were killed, thus suggesting that the disease may occur in one of approximately every 6,000 swine sent to slaughter from that part of the United States from which the animals with the lesions were obtained.

Since the lesions in the respective carcasses were observed near the end of the dressing process, when the identity of the respective viscera had been lost, it seemed desirable to obtain if possible a hog in which the infection might be demonstrated or at least suspected during life by the detection of specific agglutinins in the blood. If such an animal could be secured and properly identified before slaughter, a thorough necropsy might reveal some pertinent information and make available for additional study tissues which could not be obtained from animals killed and dressed by the routine procedure.

With this in mind, we arranged with one of the packing establishments to secure blood by tail bleeding from 102 apparently normal swine. The animals were from 8 to 10 months of age, and were selected at random from shipments of swine received from many different parts of Minnesota, Iowa and South Dakota.

Each animal was given an ear tag number, and after the blood was secured and before the animals were slaughtered, tests of agglutination were made. The results revealed agglutinins in the blood of one hog sufficient to cause agglutination of *Brucella abortus* antigen in a dilution of 1:25, whereas the blood of two other hogs caused incomplete agglutination at the same dilution. Although these titers are of questionable significance, the animals were carefully examined at necropsy, and many tissues were secured for the inoculation of guinea-pigs.¹ Lesions indicative of a specific infection were not recognized.

This phase of the problem should be investigated further, but the securing of blood from any considerable number of animals in stockyards and their retention during the time necessary to conduct a proper test of agglutination are formidable difficulties which would have to be met.

1. These animals are still living.

PATHOLOGIC CHANGES ASSOCIATED WITH THE DISEASE IN SWINE

We have no evidence that sex or breed is of significance in the occurrence of the lesions. Females and castrated males were represented in approximately equal numbers in the twenty-four swine from which our specimens were secured. Material was obtained from only one boar. The age of the animals was comparable to the general average age of hogs slaughtered in the respective abattoirs. Of the eighteen animals the approximate ages of which were recorded, seventeen were between 7 and 12 months of age, and one was 3 years of age.

The lesions, which usually are situated in the lumbar vertebrae, were disclosed in the latter stages of the dressing process when the vertebral column was split longitudinally. Previous to this operation the viscera were removed from the body, and since these were without gross alteration the identity of the carcass from which they came was soon lost. As a consequence we were able to examine the liver and spleen from only one carcass from which the lesion in the vertebra yielded an organism of the *Brucella* group. In this instance the identity of the viscera was maintained on account of an unrelated pathologic condition elsewhere in the body.

The disease represents a definite pathologic entity occurring in the vertebrae of swine which during life do not exhibit physical signs of the disease, and which at necropsy are apparently without lesions in the parenchymatous organs. The infection manifests a characteristic predilection for the bony structure of the vertebral column, and it is revealed only when the spinal column is divided longitudinally (fig. 1 *A*).

Anatomically, the situation of the lesion in twenty-three of the twenty-four hogs was as follows: lumbar vertebrae, ten; last lumbar and first sacral vertebrae (lumbosacral articulation), eight; sacral, cervical and thoracic vertebrae, each one. In two animals the lesions were multiple and occurred in the thoracic, lumbar and sacral vertebrae.

The lesion was an irregular abscess in the body of the vertebra. We never observed the occurrence of a typical lesion which ultimately yielded an organism of the *Brucella* group in the bony structure dorsal to the spinal canal. Most of the necrotic foci seemed to originate in the vertebral epiphyses, often involving the articular cartilage and the epiphyses of the adjacent vertebral structure (fig. 1 *B*). The lesion usually consisted of a single focus, but occasionally instances were noted in which foci were multiple in the same or adjacent vertebrae, and in a few cases characteristic lesions were seen in various vertebrae, extending from the cervical to the sacral region.

It was often difficult to describe the shape of the respective lesions, owing to the irregular tortuous ramifications or sinuses by which the

morbid process extended into the body of the vertebral structure and in a few instances even penetrated the overlying musculature with subsequent formation of abscesses (fig. 2).

The lesions that occurred in the lumbar vertebrae, as most of them did, often extended to the dura mater, but actual penetration of this structure and subsequent involvement of the spinal cord were not observed (fig. 1 *B*). Occasionally, however, a lesion was encountered



Fig. 1.—*A*, spondylitis of a male hog, 1½ years old (case 11). The heavily encapsulated abscess involves the body of the last lumbar and the first sacral vertebra. An organism of the *Brucella* group was obtained from the spleen of a guinea-pig inoculated with a portion of an emulsion prepared from this lesion. *B*, spondylitis of a female hog, aged 9 months (case 5). The lesion has destroyed a portion of the intervertebral disk between two lumbar vertebrae. The jagged edges of the irregularly shaped cavitation extend in one place to the spinal dura mater. The necrotic contents of the lesion were removed for animal inoculations and the making of cultures. An organism of the genus *Brucella* was obtained by direct culture from this lesion and from the spleen of guinea-pigs.

the proximity of which to the spinal canal resulted in a slight bulging into the dural space, but the encroachment was never marked.

The size of the lesions was variable. They usually measured from 0.5 to 3 cm. in their greatest diameter. The contents of the respective cavitations, although somewhat variable in character, possessed certain common features. The contents were definitely necrotic, with some differences apparent in the character of the cellular detritus. The abscessed material was grayish white to slightly yellowish, and varied from a semipurulent or thick pasty consistence to a somewhat dry,

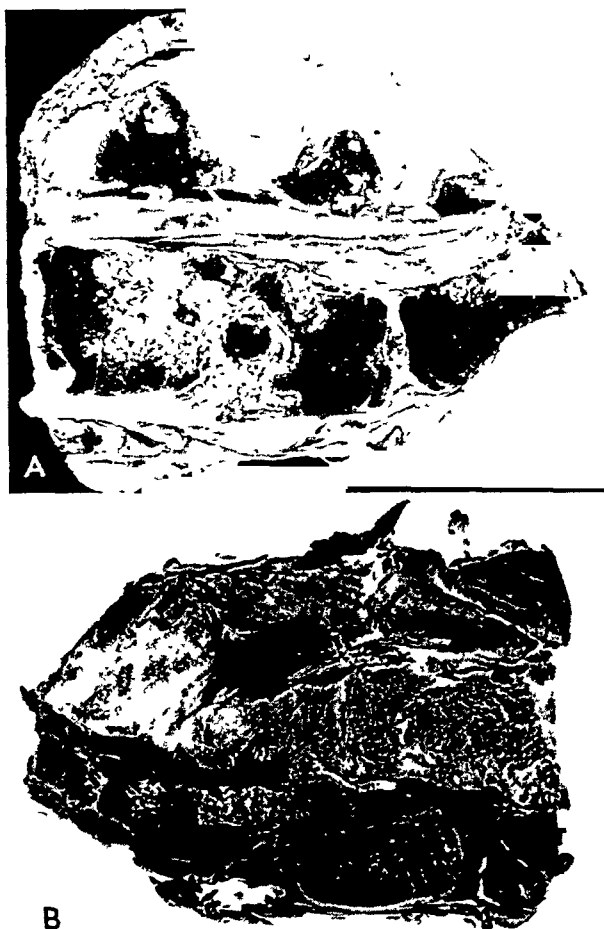


Fig. 2.—*A*, multiple lesions involving the bodies of the last two lumbar vertebrae (case 19). Much of the necrotic substance has been removed for cultures and inoculation of animals. Material from this lesion yielded bacteria of the *Brucella* group in direct culture, and induced lesions in guinea-pigs and rabbits. The morbid process extended bilaterally into the adjacent soft tissues. *B*, musculature adjacent to lesions of the vertebrae. The well encapsulated sinus, which is occupied by thick, creamy cellular detritus, communicates with the necrotic process affecting the vertebrae (same case as *A*).

caseous texture. Mineral salts were small in amount. Occasionally a lesion contained a sequestrum of bone.

The cavities were characteristically lined with a tough fibrous structure which provided a rather formidable encapsulation for many of the

abscesses. The capsular structure which was firmly adherent to the surrounding bone was most pronounced in the larger lesions, and frequently the walls were 0.3 cm. thick.

EXPERIMENTAL WORK

As the condition was encountered in different abattoirs, the diseased portion of the spinal column was removed for further examination. The procedure usually employed was as follows: The portion of bone containing the lesion was plunged into a pan of boiling water, in which it was permitted to remain for from three to five seconds.² The specimen was then removed from the boiling water, a pair of sterile sharp-pointed, curved scissors was thrust into the depths of the abscess, and as much of the material was evacuated as possible. Portions of the necrotic substance were used for the direct inoculation of culture mediums, and the remainder was used to prepare an emulsion for injection into animals.

CULTURE

In most instances from three to four tubes of the egg yolk agar medium described by Herrold³ were inoculated for the isolation and growth of *Mycobacterium tuberculosis* and a similar number of tubes of a liver infusion agar prepared by slightly modifying the procedure described by Stafseth⁴ and recommended by Huddleson.⁵

The tubes inoculated direct from the respective lesions were in most cases divided into two groups, and one group was incubated at 37 C. in a carbon dioxide

2. This was done for the purpose of reducing the possibility of extraneous contamination. The time the specimens were permitted to remain in the boiling water was not sufficient to cause a perceptible elevation of temperature in the depths of the respective abscesses, so we do not think that the procedure was of significance in those instances in which subsequent cultural attempts and inoculations of animals gave negative results. On the other hand, the possibility for extraneous contamination of the exposed portion of the respective lesions was sufficiently great to warrant a procedure which would eliminate this factor if possible. That the method was efficient is attested to by the fact that few contaminated cultures were obtained.

3. Herrold, R. D.: *J. Infect. Dis.* **48**:236, 1931.

4. Stafseth, quoted by Huddleson, I. F.; Halsey, D. E., and Torrey, J. P.: *J. Infect. Dis.* **40**:352, 1927.

5. Huddleson, I. F.: *Am. J. Pub. Health* **21**:491, 1931. The liver infusion agar is prepared as follows: Solution 1. Two pounds (0.9 Kg.) of ground, fresh beef liver is put in a flask containing 2,000 cc. of distilled water and placed in the refrigerator overnight. Without removal of the liver infusion from the flask, it is autoclaved for one hour at 15 pounds (6.8 Kg.) of pressure. From 600 to 700 cc. of the fluid portion of the autoclaved liver infusion is filtered through several layers of gauze, and after the liquid is no longer warm, 500 cc. is permitted to filter through paper. Solution 2. This consists of bacto-agar, 20 Gm.; bacto-peptone, 10 Gm.; sodium chloride, 5 Gm., and distilled water, 500 cc. The mixture is boiled for fifteen minutes, and solution 1 added. The total volume is brought to 1,000 cc., and the mixture is boiled for from two to three minutes. The pH is adjusted to 6.8, and the mixture is placed in tubes and sterilized in an autoclave under 15 pounds of steam pressure for twenty minutes.

tension of 10 per cent, while the other tubes were incubated at the same temperature under atmospheric conditions. After the third day the tubes were examined at frequent intervals, and after eight or ten days if no growth occurred, they were discarded.

In almost all instances 1 cc. of the respective emulsions was also cultured for the presence of *Mycobacterium tuberculosis*. After treatment of the inoculum with 5 per cent oxalic acid, as suggested by Corper and Uyei⁶ for the elimination of nonacid-fast bacteria, the material was seeded on four tubes of egg yolk agar proposed by Herrold.³

INOCULATION OF ANIMALS

With the exception of the material obtained from the first five cases, both rabbits and guinea-pigs were inoculated with portions of the respective emulsions prepared from the necrotic detritus secured from the different lesions. In the first five cases two guinea-pigs only were inoculated with material from each lesion, but in cases 6 to 24 inclusive, two rabbits were also inoculated. In cases 13 to 24 inclusive, three guinea-pigs were inoculated instead of two. Most of the guinea-pigs were males and were inoculated subcutaneously in the umbilical region. All the rabbits received the inoculum intravenously. The amount of emulsion injected into each guinea-pig and each rabbit was 1 cc.

The animals were permitted to live for eight weeks, after which they were killed for necropsy. At least forty-eight hours before being killed, all the guinea-pigs were given intracutaneous injections of avian and mammalian tuberculin, but in no instance was a significant allergic state elicited. At examination immediately after death, blood was secured directly from the heart for tests of agglutination,⁷ and tissue, usually the spleen, was removed aseptically for the purpose of making cultures. Tissue was also secured for subsequent histologic examination. The tissues preserved were portions of the lungs, liver, spleen, both testes and in some instances the kidneys. All sections were stained to reveal the presence of acid-fast bacteria, and if significant lesions were present duplicate sections were stained also with hematoxylin and eosin.

RESULTS

By direct culture and from the tissues of the inoculated animals, organisms belonging to the genus *Brucella* were secured from ten of the twenty-four cases studied. A summary of the attempts of culture and of the inoculation of animals in the ten cases in which positive results were obtained is given in the accompanying table.

Few of the inoculated animals died before the expiration of eight weeks, and for the most part symptoms of diseases were not evident even though subsequent necropsy disclosed the presence of well established lesions. Although many of the infected guinea-pigs from which cultures of bacteria of the genus *Brucella* were isolated exhibited multiple characteristic focal lesions in the spleen and liver, in some

6. Corper, H. J., and Uyei, N.: J. Lab. & Clin. Med. **15**:348, 1930.

7. The antigen was prepared from several strains of *Brucella abortus* and was secured from the laboratory of Dr. C. P. Fitch of the University of Minnesota. The dilutions used were: 1:25, 1:50, 1:100, 1:200, 1:400, 1:1,000, 1:1,600, 1:3,200 and 1:6,400.

instances definite anatomic alterations as a consequence of the infections were not apparent.

Differences in the virulence of the inoculums were noted in several cases. Although definite histologic lesions were noted in the spleen of one guinea-pig (case 6) and a culture of *Brucella* organism was obtained from this organ, the other guinea-pig inoculated with an equal amount of the same emulsion as the first failed to reveal the slightest evidence of disease, and attempts to obtain cultures from the splenic emulsion

Summary of the Successful Attempts to Secure Organisms of the Brucella Group From Cases of Spondylitis in Swine

Case	Site of Lesion	Direct Culture from Abscess of Bone	Guinea-Pigs			Rabbits			Comment
			Test of Agglutination	Lesions	Splenic Culture	Test of Agglutination	Lesions	Splenic Culture	
5	Lumbar vertebra	+	0*	—	+	0	0	0	Splenic culture pathogenic for additional guinea-pigs
6	Not known	Not made	0	+	+	0	+	0	One guinea-pig failed to yield a culture
8	Lumbar vertebra	+	0	+	0	0	+	0	
11	Lumbar sacral articulation	Not made	+	+	+	—	—	—	Culture obtained from only 1 guinea-pig
12	Lumbar vertebra	Not made	+	+	+	+	+	+	
13	Thoracic vertebra	+	+	+	+	+	+	+	One rabbit gave positive agglutination, but failed to yield a culture
15	Lumbosacral articulation	+	—	—	—	—	—	—	Culture of low virulence
16	Lumbosacral articulation	+	+	+	+	+	+	+	Agglutination or lesions failed to develop in 1 of the 3 guinea-pigs; cultures negative
19	Lumbar vertebra	+	+	+	+	+	+	+	One of the guinea-pigs gave positive agglutination; culture was negative
21	Lumbosacral articulation	+	+	+	+	—	—	—	

* A zero indicates that data were not available.

were unsuccessful. In case 16, although marked lesions of *Brucella* infection developed in both rabbits and in two of the three guinea-pigs given injections of an emulsion prepared from the vertebral abscess, demonstrable lesions failed to develop in the third guinea-pig of the series. Agglutinins were absent, and cultures could not be obtained from the spleen. In case 21, in which a culture of the genus *Brucella* was obtained from the vertebral lesion by direct culture, neither of the two rabbits that were given injections of the emulsion prepared from material from the lesion possessed agglutinins when killed eight weeks after exposure; lesions were not observed grossly or microscopically, and the spleens failed to yield a positive culture.

The anatomic distribution of lesions of the experimental animals was seldom widespread. In guinea-pigs the organs of predilection were the spleen and the liver. The lungs were seldom affected, and gross alterations were not observed in the kidneys. On microscopic examination many of the male guinea-pigs were found to have purulent epididymitis; often this was not apparent to the unaided eye. The infection of the epididymis was usually bilateral, but in some cases the lesions were confined to one gland. On histologic study of the tissues, a few of the animals were found to have a specific epididymo-orchitis.

The lesions in rabbits were generally in the liver and spleen. Gross involvement of the lung was observed in one case. We failed to find lesions in the joints, lymph nodes, kidneys, testes or epididymis.

Briefly, the infection in guinea-pigs was characterized by enlargement of the spleen and the occurrence of focal lesions of variable sizes in the liver. Definite foci were not uncommonly absent in the spleen, and sometimes we succeeded in obtaining an organism of the *Brucella* group from the spleen, although the only abnormality demonstrable in this organ was slight hyperplasia. The lesions were most evident in affected livers, consisting of firm grayish-white foci, varying from areas of 0.05 cm. to elevated nodules averaging 0.3 cm. in diameter. The number of lesions ranged from few to many, and in those of the smaller miliary type the resemblance to certain experimental tuberculous infections, as mentioned by Fabyan,⁸ was striking.

The spleen of infected rabbits was usually somewhat enlarged, but the presence of characteristic focal lesions was by no means consistent. When lesions were present in the spleen they were miliary, and usually measured up to 0.1 cm. in diameter. The involvement of the liver was likewise variable. Although as a rule a few focal alterations could be found in the liver of infected rabbits, occasionally necropsy revealed hundreds of lesions of the small focal or miliary type.

Microscopically, the character of the structure of the individual lesions was somewhat inconstant, depending on the duration of the infection and perhaps on the virulence of the respective bacterial cultures and their ability to overcome successfully the defense mechanism of animal tissue. The usual lesion consisted essentially of discrete, fairly well circumscribed collections of monocytic cells with a striking and characteristic tendency to assume an epithelioid appearance.⁹ The respective collections of rather large lightly staining, diffusely arranged epithelioid cells comprising the individual lesions generally revealed a caseous-like central necrosis. Incomplete encapsulation, with the occurrence of

8. Fabyan, Marshal: J. M. Research **26**:441, 1912.

9. The histopathology of the lesions induced by the different organisms of the genus *Brucella* is to constitute the subject of a subsequent contribution; hence the description of the morphologic alterations is condensed in this paper.

many lymphoid and monocytic cells, was commonly observed, and a few giant cells were often present. Calcification was not observed.

In guinea-pigs, particularly in the epididymis and occasionally in the liver and lungs, a purulent abscess-like lesion developed which differed from the small or miliary lesion in that necrobiosis had progressed to a greater degree with a corresponding diminution of the number of epithelioid cells and more complete encapsulation of the lesion. In lesions of the epididymis such as these, many of the tubules of this structure often were filled with a purulent exudate which presumably had its origin in the infective foci in nearby tissues. The testicular structure was less often involved than was the epididymis, and the morbid process, when present, was of limited extent and seemed to have its inception in the interstitial portions of the gland. The apparent predilection of the infection for the epididymis makes it imperative to include this structure when the testis of the guinea-pig is to be examined histologically for lesions of experimental infection by an organism of the *Brucella* group.

All tissues preserved from the animal used in this study were stained to disclose the presence of acid-fast bacteria, but in no instance were organisms of this character seen.

IDENTIFICATION OF THE ISOLATED BACTERIAL CULTURES

The various bacterial cultures stained lightly with Loeffler's methylene blue (methylthionine chloride, U. S. P.) and gave a negative reaction to Gram's stain. The morphology was best revealed in preparations stained for from one to two minutes in Ziehl-Neelsen's carbol-fuchsin, and examined without decolorizing. Generally the organism is best described by the term "coccobacillus." The presence of terminal granules in many of the bacteria was well brought out by the carbol-fuchsin stain. Pleomorphism was commonly observed, the variation in appearance being particularly evident in the differences in size of the organisms within the same microscopic field. Many of the longer forms had a peculiar beaded appearance. Neither spores nor capsules were observed, and the bacteria were nonmotile.

Liver infusion agar slants or the egg yolk agar medium described by Herrold inoculated with material from lesions of spontaneous spondylitis usually revealed a growth in from two to four days. The growth appeared as numerous discrete, raised colonies, irregularly circular, each with a smooth glistening surface. After prolonged incubation the respective colonies became strikingly domelike, and as growth continued, there was a tendency for many of the adjacent colonies to become confluent, which gave the growth as a whole a pebbled appearance. This feature was most noticeable on the egg yolk agar medium. Chromogenesis was not observed, the growth remaining grayish to dirty white.

Subcultures of the organisms to agar slants resulted after incubation for forty-eight hours in a moderately abundant smooth slightly grayish, glistening filiform growth with slight elevation of the edges. Subcultures thrived well in dextrose brain broth, with moderate clouding of the entire medium after incubation for seventy-two hours.

Using Meyer and ZoBell's¹⁰ modification of the so-called dye test devised by Huddleson for the differentiation of the constituent members of the *Brucella* group, we found that the various strains isolated from the cases of spondylitis which we studied grew in the presence of thionine, 1:50,000, but growth failed in the mediums containing fuchsin, 1:50,000, and pyronine, 1:200,000. Consequently, the behavior of our strains in the presence of bacteriostatic dyes indicates that the organisms belong to that group of the genus *Brucella* known as the suis type. Additional evidence that the cultures we isolated were of the suis variety was obtained from the fact that a carbon dioxide tension was not essential for the isolation and subsequent growth of the respective strains. Although excellent growths were obtained on mediums incubated in the presence of 10 per cent carbon dioxide, growths of comparable degree were likewise obtained in cultures propagated under atmospheric conditions.

For the final identification of the respective strains of bacteria obtained from the lesions of the different swine, a study was made of their antigenic properties as revealed by their ability to stimulate the production of specific agglutinins in the blood of rabbits and guinea-pigs, and by their capacity to agglutinate in the presence of specific antibodies contained in the serum of cattle affected with *Brucella abortus*.

That specific agglutinins were produced in the various animals inoculated with respective emulsions of tissue was demonstrated by the fact that every animal from which a positive culture was obtained gave definitely positive agglutination when blood serum obtained at the time the animals were killed was added to a polyvalent *Brucella* antigen obtained from Dr. C. P. Fitch of the University of Minnesota. The blood of infected guinea-pigs gave an agglutination titer of 1:200 or more, whereas the agglutination titer of infected rabbits was 1:100 or more.

Suitable antigens were prepared from each of the respective strains of bacteria isolated, and the agglutinability of each was determined by the addition of graduated dilutions of blood serum obtained from a cow found to be a marked reactor to the test for agglutination of *Brucella abortus*. All strains of the bacteria obtained from the cases of spondylitis agglutinated in the presence of blood serum from this animal in titer comparable in most instances to the results observed when the antigen secured from Dr. Fitch was used.

¹⁰ Meyer, K. F., and ZoBell, C. E.: *J. Infect. Dis.* **51**:72, 1932.

These observations pertaining to the biology of the micro-organisms obtained from abscesses of the vertebrae of swine, while in no sense comprehensive, are of sufficient significance, we believe, to justify the conclusion that the bacteria isolated belong to the genus *Brucella* and possess the salient characteristics usually attributed to the variety of the *Brucella* group known as suis.

SUPPLEMENTARY EXPERIMENTS

As the report of Krueger¹¹ indicated that organisms of the *Brucella* group could occasionally be isolated by inoculation of guinea-pigs from the lymph nodes of the mammary gland and from the diaphragmatic musculature of cattle supposedly infected with *Brucella abortus* on the basis of a positive test of agglutination, it seemed desirable to ascertain the possible infectiousness of certain tissues of swine in which lesions of spondylitis occurred. Additional tissues were therefore secured from seven of the carcasses of swine in which characteristic lesions of spondylitis were present. In the majority of instances the supplementary tissues emulsified for inoculation of guinea-pigs included portions of the muscle from the loin adjacent to the region of the lesion in the vertebra, muscle from one shoulder and bone marrow from one femur. In several cases portions of one kidney were emulsified, and in two cases inoculums were prepared from the inferior cervical and lumbar lymph nodes. In only one case was a portion of the diaphragmatic muscle secured for the inoculation of animals. From one hog portions of the spleen and liver were obtained, and attempts were made to demonstrate the presence of the specific bacterium.

Two guinea-pigs were each given injections of 1 cc. of the respective emulsions and were kept under observation for a period of eight weeks, after which they were killed and examined.

Specific agglutinins could not be demonstrated in the blood of any of the guinea-pigs used in this part of the study, and attempts to secure cultures of organisms of the *Brucella* group from the spleen failed in every instance. It should be noted, however, that cultures of the genus *Brucella* were obtained from the vertebral lesions of only three of the seven swine studied. Since the organism was not obtained from the four other animals either by direct culture or by inoculation of animals from what appeared grossly to be characteristic lesions of *Brucella* infection, it is hardly surprising that the infectiousness of apparently normal structures was not demonstrated.

COMMENT

Although we have no knowledge of the disease under consideration having been described previously, the occurrence of the lesions in the

11. Krueger, H.: *Deutsche tierärztl. Wchnschr.* **40**:481, 1932.

vertebrae of swine and their relationship to bacteria of the *Brucella* group were recorded in the annual report of the chief of the Bureau of Animal Industry of the United States Department of Agriculture for the year ending Sept. 8, 1930.¹² *Brucella abortus* of the porcine type was considered the causative agent of peculiar tuberculous-like lesions of the body of vertebrae which had been submitted to the federal laboratory from Philadelphia. The following comment was made: "Owing to the high virulence of the swine bacillus and its pathogenicity for man, these bone lesions have a special significance in meat inspection work." In the annual report of the same bureau for the year ending Aug. 31, 1931,¹³ it was stated that it had been definitely shown that these lesions are due to micro-organisms of the *Brucella* group, and that additional material studied had brought the total number of specimens yielding the organism to twenty-two. In the report for the year ending Aug. 31, 1932,¹⁴ the disease was again mentioned. Of 154 specimens that had been examined, sixty-five, or approximately 42 per cent, were found to contain viable strains of the genus *Brucella*. Specimens from which positive results were obtained were forwarded to the laboratory by representatives of the Federal Meat Inspection Service from cities in Minnesota, Iowa, Nebraska, South Dakota, Missouri, Florida and Massachusetts.

The exact geographic distribution of the disease is a matter of conjecture, since many swine slaughtered in one state originate in territory considerably removed from the abattoir. However, the finding of lesions in hogs slaughtered in such widely separated states as South Dakota, Florida and Massachusetts suggests that this specific type of *Brucella* infection is probably endemic in many different parts of the United States. What the relationship of the vertebral involvement may be to abortion disease of swine, which is an infection of the placental membranes resulting in the premature expulsion of the fetus, or to *Brucella* infection in other species is not known.¹⁵

12. Annual Report of the Chief of the United States Department of Agriculture for the Year Ending Sept. 8, 1930, p. 55.

13. Annual Report of the Chief of the United States Department of Agriculture for the Year Ending Aug. 31, 1931, p. 54.

14. Annual Report of the Chief of the United States Department of Agriculture for the Year Ending Aug. 31, 1932, p. 42.

15. Another example of an extra-uterine infection of swine by organisms of the *Brucella* group was given by James and Graham (*J. Am. Vet. M. A.* **77**:774, 1930). They described a condition in one herd of swine in Illinois which apparently had persisted on the same premises for several years. The affected animals displayed symptoms of soreness or stiffness in walking, and distinct swellings of the front and hind fetlock joints were sometimes noted. A study of the disease revealed lesions of pyemic arthritis, pyemic bursitis and osteomyelitis from which bacteria of the genus *Brucella* were isolated. The existence of spondylitis in the animals studied was not mentioned.

It seems unusual that spondylitis of swine due to bacteria of the *Brucella* group should have been recognized as a definite entity only within a relatively recent period. The apparent similarity of the disease to lesions of the bones due to *Mycobacterium tuberculosis* may frequently have obscured the true character of the lesions. The absence of reports of *Brucella* infections of this character in continental Europe may also have been due to failure to distinguish the condition from lesions of tuberculosis. Nieberle,¹⁶ in discussing tuberculous infection of the bones of domesticated animals, commented on the common occurrence of tuberculous lesions in the bones of swine in Germany, and pointed out that similar lesions were less often encountered in the bones of cattle. Nieberle mentioned that in tuberculosis of the bones of swine, the regional lymph nodes often are not diseased. These observations seem significant and suggest that perhaps some of the lesions which are considered by their gross appearance to be tuberculous are due to organisms of the genus *Brucella*.

An interesting example of the predilection of organisms of the *Brucella* group for osseous tissue was a case described recently by Kulowski and Vinke.¹⁷ The patient was an American farmer, aged 33, who had been ill for several months. He complained of pain in the lower portion of the back, had lost much weight and had had several intermittent chills and fever. Tests for agglutination of *Brucella* were definitely positive, and this with the roentgenologic examination suggested a diagnosis of "Malta fever spondylitis." By surgical means an abscess situated in the lumbar region "in front of the right lower three transverse processes" was drained, and a culture of the bovine variety of *Brucella* was isolated. Kulowski and Vinke commented on the frequency of pain low in the back as an early symptom in patients affected with undulant fever, and said that "it is reasonable to assume that spinal involvement has been frequently overlooked in the past."

Our study affords only presumptive evidence that the respective strains of *Brucella* isolated from the different specimens were responsible for the osseous lesions. Conclusive proof of the causative relationship of the specific bacterium to the resultant spondylitis must await confirmatory experimental data. Experimental work of this character is in progress and will be reported later.

Although the etiologic significance of the bacteria obtained from the different lesions may not be definitely proved, the data so far obtained in support of this contention seem convincing. The character of the lesions, the low incidence of the disease and the endemic nature of

16. Nieberle, K.: *Pathologische Anatomie und Pathogenese*, *Ergebn. d. allg. Path. u. path. Anat.* **25**:631, 1931.

17. Kulowski, J., and Vinke, T. H.: *J. A. M. A.* **99**:1656, 1932.

Brucella infections of swine are factors which suggest a specific etiology, with bacteria of the *Brucella* group the most likely culprits.

Failure to demonstrate a viable organism of etiologic significance in all of the specimens is not surprising when one considers the pathology of the disease. The lesion usually represents a more or less chronic, nonprogressive type of infection that is rather self-limiting, by virtue of the encapsulation which ensues. A structure of this kind hardly provides an optimal environment for the residence of bacteria in a living, pathogenic state, regardless of the tenacity of the micro-organisms in question. The appearance of most of the lesions studied gave a definite impression of chronicity. The duration of the respective abscesses is not known, but it is not unlikely that the majority represented a process that had its inception many months before the animal was killed. The semidry contents of some of the more thickly encapsulated lesions would certainly indicate such duration. The characteristic encapsulation of the lesion of spondylitis of swine associated with bacteria of the *Brucella* group may account for the failure of lesions to develop in parenchymatous organs such as the liver and spleen.

The evidence would suggest a hematogenous infection as responsible for the inception of the osseous lesions, although the explanation of the apparent predilection of the infection for the vertebrae of the lumbar and sacral region is not obvious.

Our experience indicates that those lesions which contain viable bacteria will yield the organism by direct culture on suitable mediums as consistently as by the more protracted and complicated procedure of isolation from the tissues of guinea-pigs previously given injections of the infective inoculums. Of course, when it is desirable to know something of the pathogenicity of the bacteria, animals must be inoculated. The inoculated animals also provide in positive cases agglutinins which are of much value in identifying the specific infection by the aid of serologic procedures.

SUMMARY AND CONCLUSIONS

A specific spondylitis of swine associated with bacteria of the genus *Brucella* is described. Lesions were obtained from twenty-four different animals, and organisms of the *Brucella* group were secured by culture and by inoculations of animals from ten. The identity of the respective cultures was determined by their behavior in experimental animals and by their antigenic properties.

The affected swine were apparently symptomless and without lesions in other parts of the body. The lesion was an encapsulated, abscess-like structure occupying an irregular cavitation in the body of the vertebra. The disease exhibited an apparent predilection for the vertebrae of the lumbar and sacral region, and adjacent vertebrae were frequently

involved. The majority of the specimens obtained were from animals less than 1 year of age, and a relationship of the lesions of the vertebrae to the usual lesions of infectious abortion in swine was not observed.

The presence in many of the necrotic foci of the vertebrae of swine of bacteria of the genus *Brucella*, which have a proved pathogenicity for guinea-pigs and rabbits, provides a possible source of infection for farmers, packing house employees, retail butchers and others who may handle pork in an uncooked state.

Dr. D. D. Tierney, Dr. George E. Totten and Dr. John L. Myers of the Meat Inspection Division of the Bureau of Animal Industry, United States Department of Agriculture, assisted in obtaining the vertebral lesions utilized in this study.

INFLUENCE OF THE INTAKE OF CALCIUM ON THE THYROID GLAND OF THE ALBINO RAT

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The present study was undertaken for the purpose of determining the influence of the intake of calcium on the thyroid gland of the albino rat under specific conditions. The theory that an excess of calcium, either sulphate or carbonate, in the drinking water derived from geological formations rich in this element is an etiologic factor in the production of goiter¹ was advanced prior to the present conception of the relationship between iodine deficiency and this condition.² Although considerable experimental evidence has accumulated to support the hypothesis of iodine deficiency, few contributions justify the earlier view. Certain observations are not in accord with either conception. Since a high incidence of goiter has been found in areas where iodine is considered to be abundant,³ and relatively few in certain limestone regions where the drinking water is turbid with suspended lime,^{1d} both opinions have been challenged.

The possibility of an interrelationship between calcium and iodine in the development of goiter was suggested by geologic studies on the distribution of iodine. Von Fellenberg⁴ pointed out that iodine tends to be leached out of soil rich in calcium. From such formations he obtained a relatively greater number of low quantitative values for iodine. On this basis it would seem reasonable to assume that the intake of people living on similar formations would not only be low in iodine, but high in calcium. Goiter occurring in such a district would be associated with an imbalance between these two elements. On this

From the Department of Medical Research, Banting Institute, University of Toronto.

1. (a) Berry, J.: *Diseases of the Thyroid Gland*, Philadelphia, P. Blakiston's Son & Co., 1901; (b) *Lancet* **1**:269, 1926. (c) Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 8, p. 436. (d) Orr, J. B., and Leitch, I.: *Iodine in Nutrition*, Medical Research Council, Special Report Series, no. 123, London, His Majesty's Stationery Office, 1929.

2. (a) McClendon, J. F., and Williams, A.: *Proc. Soc. Exper. Biol. & Med.* **20**:286, 1922-1923. (b) Marine, D.; Lenhart, C. H.; Kimball, D. P., and Rogoff, J. M.: *The Prevention of Simple Goitre*, *Bull. Western Reserve Univ.*, 1923, no. 26. (c) Orr and Leitch.^{1d}

3. Holst, J.: *Klin. Wchnschr.* **10**:118, 1931. Lunde, G.: *Canad. M. A. J.* **21**:337, 1929 (cited in editorial). Pern, S.: *New York M. J.* **115**:409, 1922.

4. von Fellenberg, cited by Orr and Leitch.^{1d}

basis, the theories of iodine deficiency and excess of calcium in the production of goiter appeared to be correlated. It was hoped that some insight into this complex problem might be gained through the present investigation.

EXPERIMENTAL OBSERVATIONS

Rats were placed in roomy wire cages with mesh bottoms, 5 animals to a cage. The cages were frequently washed and sterilized. No bedding was used. Clean coarse pine shavings were kept in the underlying trays.

Although a number of investigators⁵ have emphasized the difficulties arising from contamination of food in dietetic studies of goiter, adequate stress has not been given to the importance of segregating the animals on the low from those on the high iodine diets. Since the amount of iodine required by the rat is very small, minute traces of this element in the environment may exert considerable influence. For this reason, the majority of the animals receiving additional iodine in their food were kept in separate and remote quarters. A small number of rats on low iodine diets were housed in the same room with animals on high iodine diets, to test out this assumption.

The basic diet consisted of 76 parts of ground yellow corn, 14 parts of wheat gluten, 6 parts of wheat germ, 1 part of chemically pure sodium chloride, 1 per cent of 1 D viosterol⁶ and distilled water. Supplementing this diet, approximately 1 cc. of tomato juice per rat per day was given to render the vitamin content adequate. By analysis this food was found to contain approximately 0.003 mg. of iodine and 0.08 Gm. of calcium per hundred grams. It was employed either alone or modified by the addition of 3 per cent of chemically pure calcium carbonate or of 0.00128 Gm. of potassium iodide per hundred grams, or by a combination of both. As much food and water as the animals would voluntarily consume was given.

For the purpose of the present experiment the diets were considered to have four primary combinations: (1) low calcium-iodine content, (2) low calcium plus iodine, (3) high calcium-low iodine, (4) high calcium plus iodine.

The animals were placed on these diets at 1 month of age. A number were killed at monthly intervals, beginning at the end of the second month. The experimental period extended from December, 1931, to July, 1932.

After the desired interval had elapsed, the animals were etherized. They were incompletely exsanguinated by bleeding from the great vessels of the neck. Immediately following this procedure, the thyroid glands were secured, grossly examined and placed in a diluted solution of formaldehyde, U. S. P. (1:10). This routine excluded the possibility of postmortem changes. After adequate fixation, paraffin sections were made. Hematoxylin and eosin staining was used.

RESULTS OF STUDY

After having examined the entire series of histologic preparations of the thyroid glands from the rats, it was found necessary to develop

5. (a) Bourget, G. E.: *Am. J. Physiol.* **44**:492, 1917. (b) McCarrison, R.: *Simple Goitres*, New York, William Wood & Company, 1928. (c) McCarrison, R., and Madhava, B.: *The Life Line of the Thyroid Gland*, Calcutta, India, Thacker, Spink & Co., 1932.

6. In these studies, 1 D viosterol was obtained by diluting 250 D viosterol with the requisite amount of corn oil.

a classification in order to interpret the findings logically. Four major divisions were recognized: (1) the normal, (2) the hyperplastic, (3) the transitional and (4) the atrophic.

A typical microscopic section of a nonhyperplastic or normal thyroid gland showed it to be composed of moderate-sized acini having a rounded contour. Irregularly interspersed throughout were alveoli which varied in size and shape. These glandular elements were supported by a delicate connective tissue stroma. The vessels were not

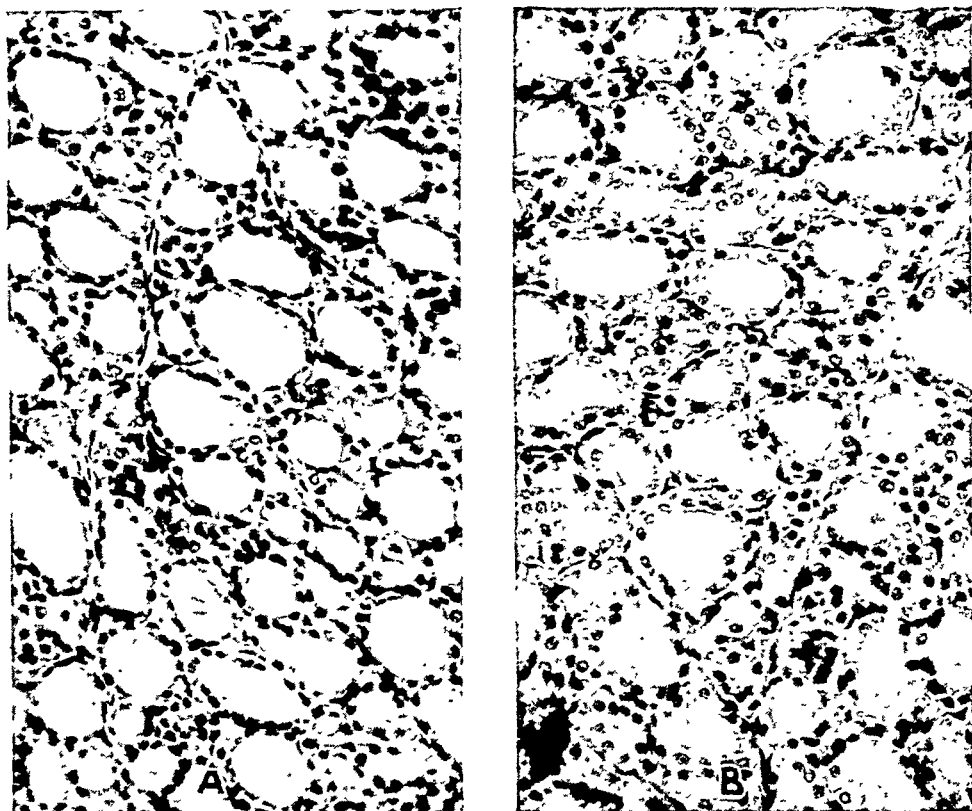


Fig. 1.—*A*, nonhyperplastic thyroid of rat receiving iodine. *B*, thyroid showing slight hyperplasia; low calcium-low iodine diet.

injected. The colloid content of the vesicles varied. The lumens of the large follicles and those of the majority of the moderate-sized follicles were entirely filled by dense bland homogeneous colloid. In others the colloid was transparent and granular. Occasionally the colloid formed a crescentic mass, occupying one side of the acinar space. It was indistinguishable in a few of the small alveoli. Slight peripheral vacuolization was observed. The epithelial cells lining the acini containing the greatest amount of colloid were very flat. Their cytoplasm was acidophilic and coarsely granular. A meager amount surrounded the intensely stained elongated nuclei. A change in the height of the

cells was noted in follicles containing lesser amounts of colloid. In a number of these follicles the lining cells became cuboidal. The cytoplasm of these cells appeared more abundant. Their nuclei were rounded and frequently showed a coarse reticular structure. A clear halo of variable size surrounded many of the nuclei. It was difficult to define the internal border of the epithelial cells in some of the alveoli, since their cytoplasm appeared to merge with the colloid content.

The microscopic appearance of the thyroid sections showed very little change with increasing age. In older animals the supporting connective tissue had an increased collagenous content. As a result, the lobular divisions were discerned more readily.

The various sections differed from one another with respect to the size of the predominating acini, the prominence of the lobular divisions, the amount of stainable colloid, the degree of vacuolization and the number of interacinar, undifferentiated cell groups. Nevertheless, despite this variability, the height of the epithelial cells never progressed beyond the low cuboidal variety; the colloid content of each section was abundant, and vascular injection was absent. These features were considered the essential requirements for placing a gland in the normal or nonhyperplastic group.

It is a known fact that the development of any pathologic abnormality is a gradual process, the stages of which blend with one another. On this basis, glands affected by hyperplasia were arranged in order of the degrees of microscopic change. The gradations were classified as slight, moderate or marked. Since each group consisted of a series of transitions characterized by a number of outstanding common features, the boundaries of individual groups were indefinite. This particular feature made the correct placing of certain specimens doubtful.

The slightly hyperplastic group was composed of glands in which there was relatively little deviation from the normal microscopic structure. On section, hypertrophy of the majority of the alveolar cells to a high cuboidal type of epithelium was noted. This was associated with a decrease in the colloid content. There was a moderate degree of vascular injection. In most of the sections the formation of new vesicles was apparent. These vesicles appeared to be arising from interacinar accumulations of undifferentiated cells.

Glands presenting hyperplasia of a moderate degree differed from the preceding group in that many of the alveoli had lost their regular contour. Small plications of the alveolar walls were frequently observed. The colloid content was greatly depleted. It was lacking from the majority of the follicles. The colloidal remnant appeared either thin, granular and vacuolated or as a network of coarse, irregular strands. Vascular injection was more conspicuous.

The markedly hyperplastic group consisted of glands in which there was a greater degree of microscopic change. The majority of sections showed the glands to be composed of enlarged acini. The acini were very irregular in size and shape. Papillomatous ingrowths were numerous. The alveoli appeared to be increased in number. It seemed probable that this increase had resulted either from papillary fusion or from budding. Stainable colloid had completely disappeared. The majority of the epithelial cells were columnar. Their cytoplasm was increased in amount, acidophilic and finely granular. The round or oval finely

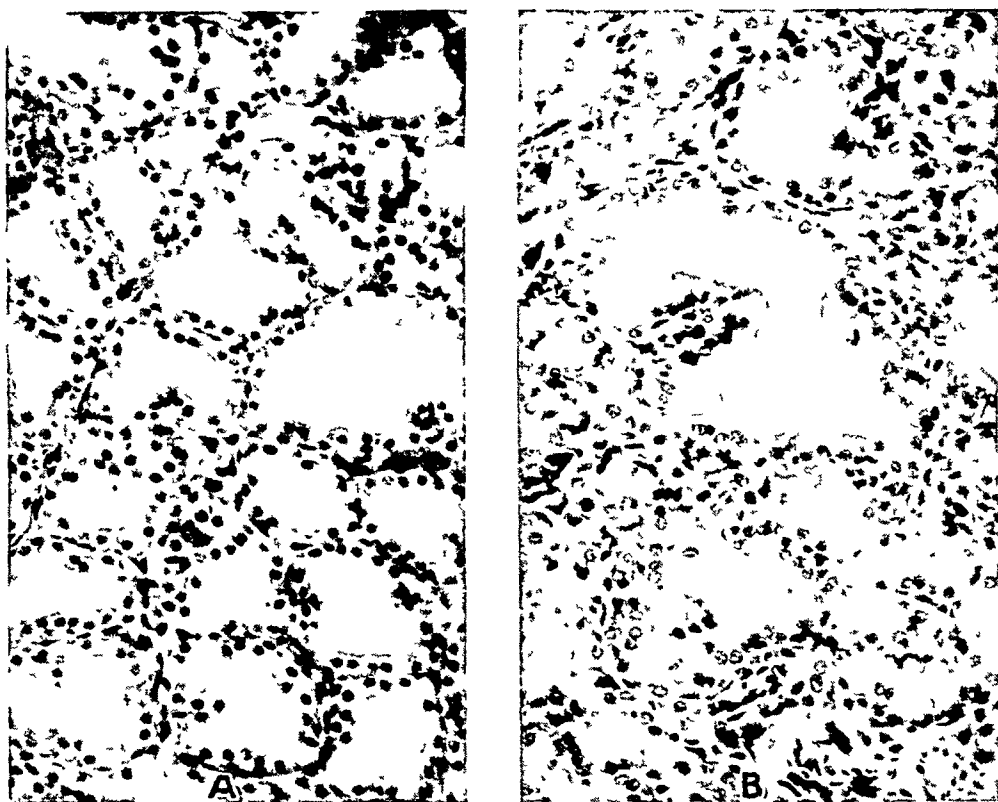


Fig. 2.—*A*, thyroid showing moderate hyperplasia, low calcium-low iodine diet
B, thyroid showing marked hyperplasia; high calcium-low iodine diet.

reticular nucleus varied in size. It usually occupied a central position within the cell. The internal border of the epithelial cells was frequently indistinct; numerous mitoses were seen. The vascular channels were greatly engorged

From the microscopic appearance of the glands studied, it was difficult to follow with any certainty the sequence of changes from the stage of hyperplasia to that of atrophy. The transitional stages were characterized by changes in both the follicles and their content. Frequently the acini were formed by degenerated epithelial cells. Enlargement was not unusual. In a number of sections meager amounts of

colloid reappeared in many of the alveoli. In some of the glands these changes were of patchy distribution.

In the majority of the thyroid glands atrophy was associated with a complete transformation in the microscopic picture. The atrophic glands showed gradations in the degree of microscopic change, as did the hyperplastic group. They fell into two groups: the early and the late atrophies.

Glands considered as showing early atrophy had completely lost their orderly structural arrangement as the result of a complete or a

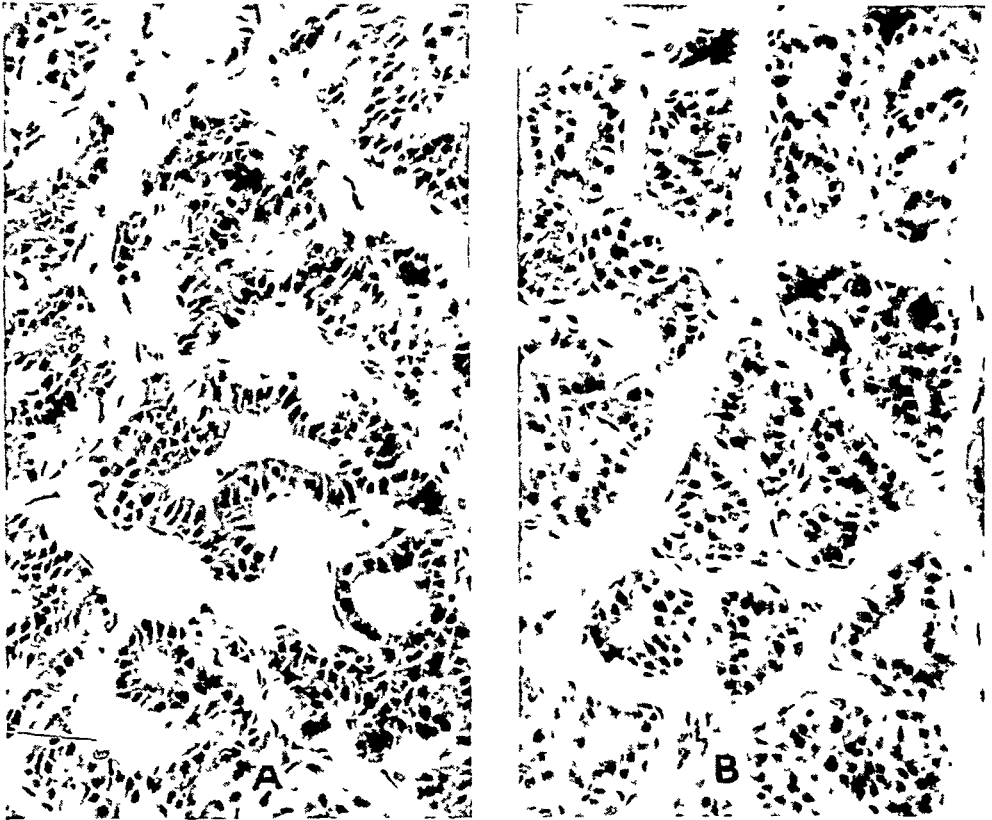


Fig. 3.—*A*, thyroid showing early atrophy; high calcium-low iodine diet. *B*, thyroid showing late atrophy; high calcium-low iodine diet.

partial collapse of the follicular structures. The epithelial elements formed irregular cords, groups or distorted acini. The previously hyperplastic alveolar cells had undergone profound degenerative changes. The nuclei appeared diversiform and intensely pyknotic. They were irregularly placed within shrunken, deeply stained cytoplasm. The cellular outlines were poorly defined. Frequently slight separation of the cells was noted. In the partially collapsed alveoli, nonvacuolated, homogeneous, dense colloid was present. Since the supporting stroma had not contracted with the follicular collapse, it was seen more readily. The vascular bed was engorged

In contrast to the early stage, late atrophy presented a bland appearance. The distorted acini were reduced in size. The majority of the epithelial columns and cellular groups had disappeared. The remaining epithelial cells appeared to be of a similar degenerative character. Most of the acini contained quite dense, nonvacuolated colloid. The vascular turgescence had subsided.

In order to avoid any personal inclination involved in evaluating the preparations, they were first arranged according to the foregoing classification, without knowledge of the experimental group to which a specimen belonged. This relationship was later determined.

From the results indicated in table 1 it will be seen that hyperplastic thyroid glands were found in 67 per cent of 24 animals maintained on the low calcium-low iodine diet for a period of two months. In 54 per cent of these the degree of response was slight, and in 13 per cent it was moderate. The remainder of the glands were considered within

TABLE 1.—Changes in the Thyroid Gland Occurring in Rats on Low Iodine Diets

Diet	Time on Diet, Mos.	Number of Animals	Changes in Thyroid Gland						
			Normal, per Cent	Hyperplasia			Transitional, per Cent	Atrophy	
				Slight, per Cent	Moderate, per Cent	Marked, per Cent		Early, per Cent	Late, per Cent
Low calcium.....	2	24	33	54	13
High calcium.....	2	35	9	91
Low calcium.....	3-7	33	6.1	..	72.7	9.1	12.1
High calcium.....	3-7	35	56.6	17.1	17.1	8.5

the normal range. In contrast, 100 per cent of the group of 35 animals on the high calcium-low iodine diet had hyperplastic glands. Not only were all the glands hyperplastic, but the response was excessive in comparison with that in the preceding group on the low calcium diet. Marked changes were found in 91 per cent of these. A lesser degree of response was shown in the remaining 9 per cent.

Retrogressive changes became manifest in a number of specimens obtained at the end of the third month from animals on low iodine regimens. Ninety-three and nine-tenths per cent of 33 animals on the low calcium-low iodine diet and 43.4 per cent of 35 animals on the high calcium-low iodine diet showed these pathologic abnormalities throughout the experimental period. The percentage difference between the groups on the low iodine diet was due to the persistence of hyperplasia in rats receiving additional calcium. Since transitional phases of the retrograde phenomena affected the majority of animals on the low calcium-low iodine diet, it seems that the conditions in this group favored regression. Conversely, in the group on the high calcium-low iodine diet, the prerequisites tended to retard the onset of similar manifestations.

Attention has previously been directed to the difficulty of following the consecutive microscopic stages in the transformation from hyperplasia to early atrophy. Following the careful examination of sections placed in the transitional group, the occurrence of certain trends in the response of the animals on the same diet was indicated. The essential difference between the two groups was related to the reappearance of colloid in rats on the low calcium-low iodine diet. In these specimens, small amounts of thin colloid were observed within the lumens of some of the hyperplastic follicles situated in the periphery of the sections. Nuclear and cytoplasmic degenerations developed secondarily in the follicular epithelium. The amount of colloid observed was considered inadequate to prevent the later acinar collapse.

Aside from the foregoing changes, another type of reaction was observed in a number of specimens from animals that had been on the same diet for from five to seven months. Thin granular colloid appeared in a considerable number of the alveoli the epithelial cells of which showed little hypertrophy. In one of the oldest specimens, this accumulation had been focal, microscopically resembling an adenoma. In contrast, the earliest retrograde phenomenon recognized in glands from animals on the high calcium-low iodine diet was the presence of small groups of enlarged acini lying in the periphery. These follicles were formed by degenerated epithelial cells having pyknotic nuclei of variable size embedded in intensely stained, shrunken cytoplasm. In some of the sections, similar cellular degenerations were observed in alveoli of the usual size. Infrequently small amounts of stainable colloid were seen within the lumens of these acini.

Approximately the same number of atrophic glands were found in both groups of animals on low iodine diets. The two groups differed, however, in the degree of atrophy. In rats on the low calcium-low iodine diet, early and late atrophy appeared with about the same frequency. A relative increase in the early atrophic lesions was shown in the group on the high calcium-low iodine diet. No correlation existed between the degree of atrophy found in glands from animals within the same experimental group and the duration of the deficiency.

The thyroid glands of 106 animals on similar diets supplemented by potassium iodide were examined at corresponding monthly periods. These glands invariably had a nonhyperplastic structure. No increase in the colloid content was demonstrable in the glands of animals on the high calcium diet with added iodine.

In planning the work, the importance of widely separating rats on low iodine diets from others receiving supplemental iodine was considered. The findings recorded in table 2 showed that diets capable of producing marked hyperplasia of the thyroid gland in the majority of

segregated animals gave rise to decreased or irregular reactions in the nonsegregated group. From these results it is evident that many of the latter group were acquiring additional iodine. The source was either from a certain amount of sublimation from the food with a high iodine content supplied in open dishes in nearby cages or through inadvertent contamination. These observations suggest that a low intake of iodine can be relied on only in animals widely separated from others receiving iodine in their diets.

After having made a careful histologic survey of the various specimens, the question arose concerning the relationship of these findings to the macroscopic appearance. In the gross, the normal or nonhyperplastic glands were small and pale pinkish gray. The isthmus was usually indistinct. With increasing cellular activity the glands gradually enlarged and assumed a dark grayish-pink color. The isthmus was readily seen. The small superficial ramifications of the vascular chan-

TABLE 2.—*Influence of Segregation on the Initiation of Changes in the Thyroid Glands of Rats on Similar Diets*

Number of Animals	Time on Diet, Months	Conditions	Changes in Thyroid Gland				With Colloid Retention, per Cent
			Normal, per Cent	Slight, per Cent	Moderate, per Cent	Marked, per Cent	
21	2	Not segregated	9	38	14	14	25
35	2	Segregated	9	91	..

nels began to appear. Grossly, glands presenting microscopic evidence of marked hyperplasia were greatly enlarged and a deep congested red. Their surfaces frequently appeared finely granular. Greatly engorged, tortuous vessels stood out like whipcords on the gland. The isthmus appeared as a thin dark red band. The thyroid tissue was quite friable. The atrophic glands had a macroscopic appearance indistinguishable from either the hyperplastic or the normal groups. The atrophies classified as early could not be differentiated in the gross from changes graded as markedly hyperplastic. A gradual approach toward the normal macroscopic appearance became evident in glands in which there was microscopic regression toward the late atrophic state. Based on these observations, interpretation of the activity of the thyroid gland of the rat from the gross appearance alone should be made with caution.

COMMENT

Investigators concede that the thyroid gland responds to a variety of stimuli. Of these stimuli, deficiencies and excesses in certain elements contained in the food have received attention. Although the majority of workers have reported that the lack of iodine brings about

an enlargement with hyperplasia of the thyroid gland of the rat,⁷ a small number have failed to confirm this observation.⁸ The findings in the present study indicated the essential importance of segregation in dietetic experiments in which the final results are dependent on variations in the intake of iodine.

The problem of an unknown etiologic factor affecting investigations on goiter produced experimentally in areas of endemic goiter has been repeatedly raised. Since the production of goiter in rats on the Steenbock rachitogenic diet has recently been demonstrated not only in this endemic zone,⁹ but also in a goiter-free district,^{7c} such an influence was considered to be precluded from the present study.

The finding of variations in the histologic structure of the thyroid glands of rats in both the normal and the pathologic groups was usual and unavoidable.¹⁰ Such influences as individual susceptibility, transient physiologic demands, unrecognized intercurrent infections, sex, size, season, intake of food and differences in the composition of food (e. g., new grains, inadequate mixing) have some effect in producing these variations. In any biologic test such factors should not be entirely disregarded. In view of the limited knowledge, it seems impossible to estimate just how much of the response to attribute to each agent.

The findings in this study further substantiated the previous observation that the addition of small amounts of iodine counteracted the effect of diets capable of producing hyperplasia of the thyroid gland of the rat.^{7h} These results, however, were not in accord with certain recent views expressed in the literature relative to human consumption of iodized salt. The opinions that the increased incidence of toxic goiter in human beings may be directly related to the use of iodine in some cases,¹¹ and that the close supervision of those to whom iodine is

7. (a) Drennan, A. M.; Malcolm, J., and Cox, G. A.: *Brit. J. Exper. Path.* **12**:430, 1931; (b) Hayden, E. M.; Wenner, W. T., and Rucker, C. W.: *Proc. Soc. Exper. Biol. & Med.* **21**:546, 1923-1924; (c) Krause, W. E., and Monroe, C. F.: *J. Biol. Chem.* **89**:581, 1930. (d) McClendon and Williams.^{2a} (e) Remington, R. E.: *J. Biol. Chem.* **97**:cr, 1932. (f) Sorour, M. F.: *Beitr. z. path. Anat. u. z. allg. Path.* **71**:267, 1923. (g) Tanabe, H.: *ibid.* **73**:415, 1925. (h) Thompson, J.: *J. Nutrition* **5**:359, 1932. (i) Levine, Harold: *J. Biol. Chem.* **97**:c, 1932.

8. (a) Hellwig, C. A.: *Arch. Path.* **11**:709, 1931. (b) Jackson, C. M., and P'an, M. T.: *Endocrinology* **16**:146, 1932.

9. Krause and Monroe.^{7c} Thompson.^{7h}

10. Marine, Lenhart, Kimball and Rogoff.^{2b} McCarrison and Madhava.^{5c}

11. Bircher, E.: *Beitr. z. klin. Chir.* **141**:580, 1927. Jones, D. W. C.: *Proc. Roy. Soc. Med.* **21**:1217, 1928. Ledoux, E.: *Rev. de méd.* **41**:225, 1924. McClure, R. D.: *J. A. M. A.* **88**:595, 1927. Maurer, E.: *Ztschr. f. Ernähr.* **1**:267, 1931. Potter, E. B., and Morris, W. R.: *Tr. Am. A. Study Goitre*, 1932. Raab, W.: *Wien. klin. Wchnschr.* **44**:309, 1931. Vienna Foreign Letter, J. A. M. A. **96**:1522, 1931. Zimmermann, H.: *München. med. Wchnschr.* **78**:52, 1931.

being administered as a preventive measure is desirable,¹² lead one to believe that small amounts of iodine may not be entirely harmless. In contrast to the preceding evidence, goiter has been reported to develop in rats maintained on diets containing large amounts of iodine.¹³ Whether these findings may be attributed to the iodine per se seems questionable in view of the beneficial effects on the growth of rats reported by Hanzlik and his co-workers,¹⁴ who used comparable amounts of iodine in so-called complete and deficient diets. The lack of deleterious effects in the present study following the daily consumption of the iodine-containing diets by the rats over a period of seven months afforded speculation. These divergent findings may in part be due to the following possible factors: of the human beings affected, a number had definitely or incipiently pathologic changes in their glands prior to the use of iodized salt; the present experiment was of insufficient duration; the tolerance of the rat for iodine is relatively greater than that of man; a disproportion existed between the inorganic or organic constituents of the human intake of food. It must be conceded, however, that the conditions in the animals on the high calcium plus iodine diet were considered to favor the development of a goitrous process. The negative results on this diet may be related to the dosage, the amount used being insufficient to promote the manifestations reported from the exhibition of large doses of iodine to rats, although adequate to inhibit the influence of calcium.

A renewed interest in the relation of calcium to goiter has been taken by a few investigators. Tanabe^{7g} and Thompson^{7h} recently reported experiments which suggest that the addition of calcium enhances the degree of hyperplasia occurring in rats on low iodine diets. Hellwig,^{8a} repeating Tanabe's work, found that calcium added to the drinking water initiated hyperplasia in the rat. Wilms¹⁵ observed that water from goitrous districts lost its activity after precipitation of its calcium by boiling. Although Sorour,^{7f} Remington,^{7e} Levine⁷ⁱ and Drennan, Malcolm and Cox^{7a} did not emphasize the fact, their findings showed that hyperplastic changes resulted in animals maintained on high calcium-low iodine diets. In contrast, McCarrison and Madhava^{5c} found that the addition of small amounts of lime to mixed diets produced an increase storage of colloid in rats and pigeons. This observation was supported by Kottman's¹⁶ opinion that calcium increased the viscosity of the colloid in the thyroid gland.

12. McCreary, J. B.: *Pennsylvania M. J.* **34**:189, 1930.

13. Spence, A. W.: *Brit. J. Exper. Path.* **13**:157, 1932. McCarrison and Madhava.^{5c}

14. Hanzlik, P. J.; Talbot, E. P., and Gibson, E. E.: *Arch. Int. Med.* **42**:579, 1928.

15. Wilms, M.: *Deutsche med. Wchnschr.* **36**:604, 1910.

16. Kottman, cited by Hellwig.^{8a}

Aside from the preceding pathologic evidence, other investigations have indicated that disturbances occur in the calcium metabolism of patients with hyperthyroidism, and that such disturbances occur following the administration of thyroid preparations to man and to animals. These disturbances were evidenced in an excessive elimination of calcium.¹⁷ Aub and his co-workers^{17a} were of the opinion that the excessive calcium was derived from the bony depots. That decalcification of the bones has been frequently demonstrated in long-standing cases of hyperthyroidism,¹⁸ and that the addition of thyroid to a borderline rachitogenic diet made the diet definitely rachitogenic¹⁹ favored this view. Some unpublished results have shown that a longer period was required to produce marked rickets in rats when a small amount of iodine was added to a low iodine, rachitogenic diet capable of initiating marked rickets in three weeks. This observation added further support to Aub's suggestion. The metabolic studies of Abelin²⁰ demonstrated that calcium carbonate lowered the action of thyroxine in rats.

In an attempt to gain an insight into the results obtained in the present study, certain factors relative to the absorption of calcium and iodine were considered. In this connection the acid-base value of diets has been thought of importance.²¹ It has been suggested that a preponderance of alkali over acid elements in diets, as well as in the products of digestion, may interfere with the absorption of these elements through increasing the alkalinity of the intestinal contents. In the experimental diets employed in this study, the addition of 3 per cent calcium carbonate necessarily involved a greater relative alkalinity in comparison with the basal diet. Redman, Willimott and Wokes^{21c} and McRobert²² showed that the gastro-intestinal tract of the average adult rat is acid, although McRobert²² indicated that a small portion of the lower part of the ileum is usually alkaline. This alkalinity could be prevented by adding certain foods to the diet, among which were

17. (a) Aub, J. C.; Bauer, W.; Heath, C., and Robes, M.: *J. Clin. Investigation* **7**:97, 1929. (b) Kummer, R. H., cited by Aub, Bauer, Heath and Robes. (c) Parhon, M., cited by Aub, Bauer, Heath and Robes. (d) Peters, J. P.: *Am. J. Surg.* **10**:530, 1930. (e) Scholz, W.: *Ztschr. f. exper. Path. u. Therap.* **2**:271, 1905.

18. Aub, Bauer, Heath and Robes.^{17a} Dunlap, H. F., and Moore, A. B.: *M. Clin. North America* **12**:1511, 1929. Plummer, W. A., and Dunlap, H. F.: *Proc. Staff Meet. Mayo Clin.* **3**:119, 1928.

19. Mellanby, E.: *J. Physiol.* **57**:ii, 1923.

20. Abelin, I.: *Biol. Abstr.* **3**:18587, 1929.

21. (a) Bauer, W.; Albright, F., and Aub, J. C.: *J. Clin. Investigation* **7**:75, 1929. (b) Farquharson, R. F.; Salter, W.; Tibbetts, D. M., and Aub, J. C.: *ibid.* **10**:221, 1931. (c) Redman, T.; Willimott, S. G., and Wokes, S.: *Biochem. J.* **21**:589, 1927.

22. McRobert, G. R.: *Indian J. M. Research* **16**:545, 1928.

tomatoes; this directly applies to the diets employed in this study. That the acid-base value of the diets in this study affected the p_H of the intestine in these experiments was considered doubtful, since the contents from different parts of the tract were examined from time to time, and in no instance did the p_H exceed 6.8. Stewart and Percival²³ stated that the calcium ions remain free as long as the p_H remains below 7. Iodine molecules have been considered more free in an acid medium. Greenbaum and Raiziss²⁴ showed that while potassium and sodium iodide were almost entirely excreted by the kidney, calcium iodide differed, approximately half appearing in the urine, and the remainder being eliminated with the feces. The preceding observations indicate that the gastro-intestinal tracts of the experimental animals presented conditions favorable and unfavorable for the assimilation of calcium and iodine. In all of the experimental animals the acidity of the contents of the intestine favored the availability of both calcium and iodine. Utilization might have been interfered with by the formation of calcium iodide in diets containing a large amount of calcium. In such a dietary study, the balance between these factors will be involved.

The tentative deductions suggested are as follows: Other factors being constant, the largest amount of iodine would be assimilated from diets low in calcium; a relatively greater iodine deficiency would be likely to occur in animals receiving a low iodine diet containing large amounts of calcium; an increased amount of iodine would be necessary to meet the body's requirement if there was an associated high consumption of calcium.

The importance of the inorganic composition of diets in relation to organic function is becoming increasingly recognized. When certain mineral elements are unbalanced, characteristic pathologic abnormalities develop.²⁵ On this basis, the existence of a balance between iodine and calcium might be considered.

An explanation of the association of iodine and calcium with changes in the thyroid gland involved the hypothesis that there must be a definite equilibrium of these two elements within the body to insure normal function of the thyroid gland. Since a considerable range of individual variation of the elements in a mineral balance may occur prior to the appearance of signs or symptoms referable to a disturbance, a certain degree of fluctuation must be recognized in relation to the iodine-calcium balance. Furthermore, if a disproportion exists in an

23. Stewart, C. P., and Percival, G. H.: *Physiol. Rev.* **8**:283, 1928.

24. Greenbaum, F. R., and Raiziss, G. W.: *J. Pharmacol. & Exper. Therap.* **30**:407, 1927.

25. McCollum, E. V., and Simmonds, N.: *The Newer Knowledge of Nutrition*, ed. 4, New York, The Macmillan Company, 1929.

elemental balance, an attempt is made by the body to reestablish an equilibrium by mobilizing any available reserves. From this it follows that a disturbance of the balance between iodine and calcium beyond certain limits is associated with the goitrous state. The results obtained in this and in other studies previously noted, in which disturbances in the calcium metabolism were found in conjunction with abnormalities of the thyroid gland, have lent credence to this view.

In applying this theory to the present results, it will be recalled that if the available iodine is reduced by feeding a low iodine diet, the activity of the thyroid gland is increased in an attempt to supply the necessary requirement of synthetic iodine compounds. Microscopically, this is evidenced by a decrease in stainable colloid, hypertrophy and hyperplasia of the cellular elements. The amount of change has been related more or less closely to the duration and the degree of the deficiency. If, in addition, a balance between iodine and calcium has to be maintained, an associated increase in calcium exerts a further stimulating effect on an already overworking gland. The experimental findings in animals on the high-calcium-low iodine diet supported this assumption. A deficient intake of both elements induced less marked changes in the thyroid glands of animals on the low calcium-low iodine diet. In this instance, although a response was to be expected owing to the deficiency of iodine per se, the factor of equilibrium exerted little influence. In relation to the group on low calcium plus iodine diet, it must be admitted that the results were inconclusive, since the animals were carried on this diet for only two months. In this group the balance may have been disturbed or it may have been normal. If it was abnormal, the calcium reserves sufficed to maintain equilibrium throughout the experimental period. On the other hand, the fluctuation in iodine may have been within the range of the balance. The finding of nonhyperplastic glands in animals on the high calcium plus iodine diet was explicable on this hypothesis. In this diet, although the quantity of both constituents doubtless exceeded the normal requirements, the balance was maintained at a higher level.

SUMMARY

The thyroid glands of 254 rats have been studied under experimental conditions. The gross manifestations were frequently misleading criteria on which to base an opinion regarding the histologic state of the thyroid gland.

In animals on diets deficient in iodine there was a gross enlargement of the gland associated with hypertrophy and hyperplasia. In some cases this condition had subsequently reverted to atrophy. The addition of calcium carbonate to diets similarly deficient in iodine resulted

in a greater and more rapid increase in the size of the gland, as well as in a more marked acinar hyperplasia. The addition of a small amount of iodine to the diets prevented the development of hyperplasia.

The experimental evidence was considered indicative of an intimate interrelationship between iodine and calcium in the production of goiter. On this basis, the theories of the incitation of goiter by deficiency of iodine and an excess of calcium appeared to be correlated.

EXPERIMENTAL PATHOLOGY OF THE LIVER

XII. EFFECTS OF FEEDING DESICCATED THYROID GLAND ON RESTORATION OF THE LIVER

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The ability of the liver to restore a normal amount of parenchyma following loss sustained either by partial surgical removal or by pathologic changes is well known, but the physiologic factors which induce such rapid recovery are as yet imperfectly understood. Recent observations on the dog, white rat and chicken seem to indicate that restoration may be correlated with the volume of blood entering the hepatic remnant. When a large portion of hepatic parenchyma is removed, the available hepatic capillary bed for the portal blood is correspondingly reduced, whereas the volume of blood in the portal vein remains essentially the same.

Data on the restoration of the livers of rats maintained on various diets give evidence of considerable difference in the amount of parenchyma restored. These data, too, may be correlated, not so much with the factors related to diet, but with the volume of blood entering the liver through the portal vein. This report is based on the results obtained in a study of the restoration of the liver in rats maintained on a standard ration to which had been added small portions of desiccated thyroid gland.

EXPERIMENTAL METHODS

Attempts were first made to develop a condition of hyperthyroidism by the subcutaneous injection of thyroxine. Normal, healthy rats, which were on a standard ration, and the daily weights of which were increasing, were given doses of 0.5 mg. of thyroxine daily. Loss of weight and other indications of increased metabolic activity were apparent in a few days, but immediately after the surgical removal of 75 per cent of the liver each of these rats died. In a second series of rats hepatectomy was performed before marked effects of thyroxine were induced; again each of the rats died immediately after partial removal of the liver. Accordingly, thyroxine was discontinued, and 1 per cent by weight of desiccated thyroid gland was added to the normal ration to induce characteristic changes. The data on the daily consumption of food indicated that each rat consumed about 150 mg. of the dried gland each day. Eighteen rats were then isolated for two weeks, fed the standard ration and weighed every two days. During this period the

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rats increased in weight from an average of 169.3 to 195.6 Gm. The thyroid ration was then added to the diet, and a decrease in the weight of the body was soon observed. After a week of this dietary regimen, the usual hepatic component was removed from each rat. Here again, as when thyroxine had been given, the rats died immediately after operation. Thus these preliminary experiments proved that rats in which hyperthyroidism had been induced either by the ingestion of thyroxine or by the administration of desiccated thyroid gland could not withstand the loss of 70 per cent of the liver.

In order to secure data concerning restoration of the liver when the rat was subjected to the effects of desiccated thyroid gland, the liver was partially removed before feeding with the gland was commenced. Fifty-four rats, aged from 6 to 8 months, were isolated, maintained on the standard ration and subjected to partial hepatectomy. Immediately afterward, the rats were placed on the standard ration to which was added the 1 per cent desiccated thyroid gland; they continued to eat this during the period of observation. Groups of five rats each were killed by exsanguination after three, seven, fourteen, twenty-one and twenty-eight days, respectively; the weight of the restored parenchyma was determined, and the ratio of the weight of the liver to the weight of the body was computed for each rat. As a basis of comparison, a series of rats, comparable in every way with those operated on, were placed on an identical thyroid ration and were killed at corresponding intervals, in order to secure data on the weight of the liver and on the ratio of the weight of the liver to the weight of the body of the rat not operated on during the period of experimental observation.

To establish satisfactory control data on the weights of the livers and the weights of the rats, twenty-five rats ranging in weight from 128 to 214 Gm., with an average body weight of 156.04 ± 2.684 Gm., were killed. The average weight of the livers of this control group was 6.576 ± 0.3890 Gm., and the average ratio of the weight of the liver to the weight of the body was 0.0421. From a knowledge of averages, standard deviations and correlation coefficients, a linear equation was computed, which would describe one variable in terms of the other. If x was the weight of body and y the weight of liver, then y was computed to be $0.0505 x - 1.302 \pm \frac{0.3800}{\sqrt{n-1}}$ Gm. With this equation, therefore, the preoperative weight of the liver was computed on the basis of the preoperative weight of the body for each rat experimented on.

EXPERIMENTAL OBSERVATIONS

All data for this study have been condensed (table 1, charts 1 and 2). All the rats lost weight because of the onset of hyperthyroidism. Rats killed had lost weight as follows: at the end of the third day, 9.5 per cent of their original weight; at the end of the seventh day, 18.5 per cent; on the fourteenth day, 15.1 per cent; on the twenty-first day, 18.4 per cent, and on the twenty-eighth day, 14.6 per cent. Other features such as rough coat and hypersensitiveness were noted; diarrhea was not observed. Since all the rats lost weight, it seemed desirable to compute the amount of liver restored after partial removal, not only in grams, but in percentages related to the preoperative weight and the attained weight of the body.

The weights of the livers recorded at the end of the third day after partial removal indicated that the restorative process in the thyroid-fed rats was well under way, although it was no greater in these rats than in rats fed normal rations (chart 1). At the end of the first week, however, the livers of the thyroid-fed rats manifested some increase in restoration over those serving as controls. On the basis of the original, or preoperative, weight of the body, the thyroid-fed rat had a hepatic parenchyma of 2.8 Gm. per hundred grams of body weight as against

TABLE 1.—*Summary of Data on Restoration of the Livers of Rats Given Desiccated Thyroid Gland with the Ration*

Group	Weight of Animal Prior to Partial Hepatectomy, Gm.	Weight of Liver* Prior to Partial Hepatectomy, Gm.	Liver Removed at Operation, Gm.	Liver Remaining After Partial Hepatectomy, Gm.	Weight of Body When Rat Was Killed, Gm.	Weight of Liver When Rat Was Killed, Gm.	Actual Increase of Liver During Restoration, Gm.	Weight of Liver During Restoration, per Cent of Body Weight	
								Pre-operative	Post-operative
Rats operated on (54).....	168.3± 2.41	7.197± 0.052	4.09± 0.080	3.107± 0.095					
72 hours post-operatively	165.0± 10.80	7.030± 0.190	4.26± 0.395	2.770± 0.439	149.2± 10.78	4.12± 0.233	1.350± 0.497	0.025	0.027
7 days post-operatively	157.9± 4.52	6.671± 0.190	4.14± 0.126	2.531± 0.228	128.6± 6.11	4.40± 0.067	1.869± 0.237	0.028	0.034
14 days post-operatively	155.6± 3.55	6.555± 0.190	3.32± 0.148	3.235± 0.241	132.0± 4.65	6.78± 0.269	3.545± 0.361	0.043	0.051
21 days post-operatively	181.4± 9.67	7.858± 0.190	4.36± 0.273	3.498± 0.332	148.0± 11.38	8.10± 0.849	4.602± 0.912	0.045	0.054
28 days post-operatively	176.4± 2.93	6.596± 0.190	3.90± 0.091	2.696± 0.210	133.6± 3.17	7.52± 0.219	4.824± 0.303	0.048	0.056

* Regression formula: Weight of liver = 0.0505 (weight of body) — 1.302 ± $\frac{0.3800}{\sqrt{n-1}}$ Gm.

2.7 Gm. in the control series. From this time on, the discrepancy in the two curves representing the extent of hepatic restoration in the two series of rats was all the more marked (chart 1). The average weight of the livers of the thyroid-fed rats killed after fourteen days was 4.3 Gm. as against 3.2 Gm. recorded as the average weight when rats were fed the ration without the desiccated gland. From the fourteenth to the twenty-eighth day, the curves are roughly parallel, and at the end of the fourth week of restoration the average weight of the livers was 4.9 Gm. for the rats fed on thyroid gland in contrast to 4 Gm. for the control rats. The impetus to more rapid restoration when the rats were

fed the thyroid ration occurred some time during the second week, after which the rate of recovery was more or less constant.

When the percentage of the amount of parenchyma restored in relation to the weight of the rat was considered, a similar divergence between the livers of rats on the normal ration and the livers of the rats on the thyroid ration was apparent. In chart 2 the ratio of the amount of parenchyma to the preoperative weight and that to the attained weight of the body are plotted. The changes in the liver were considered on the basis of the preoperative weight of the body, as the decrease in the weight of the rats was slightly more in those fed

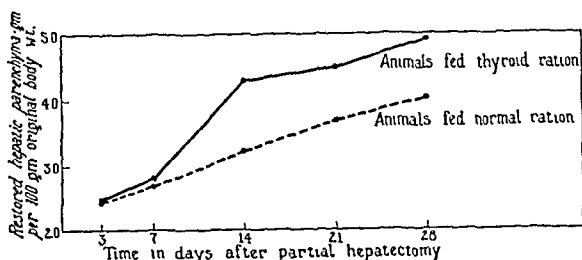


Chart 1.—Comparison of the average percentage weight of the livers of partially hepatectomized rats fed a thyroid ration with the average percentage weight of the livers of partially hepatectomized rats fed a normal ration.

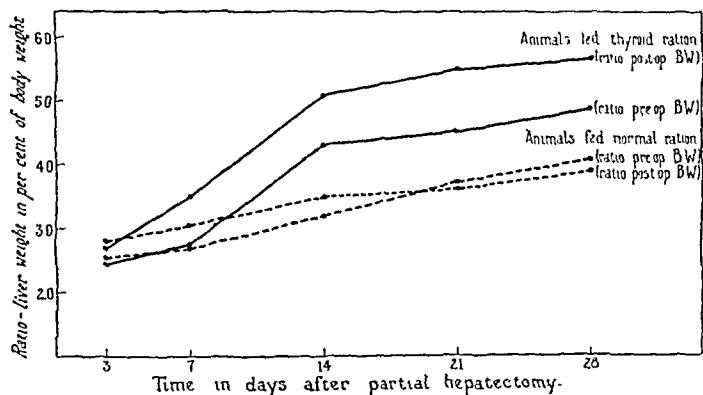


Chart 2. —Ratios of the weight of the liver to the weight of the body during restoration.

the desiccated thyroid gland. The curve of these ratios (chart 2) from determinations made at three, seven, fourteen, twenty-one and twenty-eight days after partial hepatectomy shows clearly that the average increase in weight of the livers was considerably greater for each unit of body weight when the rats were fed the desiccated gland. This is true whether these percentages were computed on the basis of the preoperative weights of the rats or on the basis of their weights at the time they were killed. A real discrepancy between the curves was not apparent until the fourteenth day. On the third day, the percentages

in the two groups were more or less alike, and at the end of the week the percentages of the weights of the livers being restored computed on the basis of the average weight of the animals just prior to operation were essentially alike in the rats fed on thyroid gland and in the normal control rats. The gain in the average percentage of weight of liver in relation to weight of body attained at the fourteenth day by the rats fed on thyroid gland was maintained to the end of the experiment, when there was an average ratio of 0.048 in contrast to 0.041 among the control animals operated on. Accordingly, it seemed that the maintenance of partially hepatectomized rats on a thyroid diet increased the extent of restoration of the liver.

TABLE 2.—Changes in Average Weight of Livers of Rats not Operated on Maintained on Thyroid Ration

Group	Number	Weight of Body, Gm.	Estimated* Weight of Liver, Gm.	Weight of Liver When Rat Was Killed	Change in Weight of Liver, Gm.	Percentage of Weight of Liver in Relation to Original Weight of Body
All animals	20	153.8 ± 2.200	6.465 ± 0.0850	0.0420
7 days.....	5	142 ± 6.101	5.869 ± 0.1900	5.760 ± 0.1780	-0.109 ± 0.2603	0.0405
14 days.....	5	159 ± 5.127	6.707 ± 0.1900	7.070 ± 0.5598	+0.363 ± 0.5911	0.0445
21 days.....	5	157 ± 5.102	6.626 ± 0.1900	7.760 ± 0.2171	+1.134 ± 0.2884	0.0494
28 days.....	5	157 ± 5.352	6.626 ± 0.1900	7.880 ± 0.1545	+1.254 ± 0.2449	0.0502

* Regression formula: Weight of liver = 0.0505 (weight of body) - 1.302 ± $\frac{0.3800}{\sqrt{n-1}}$ Gm.

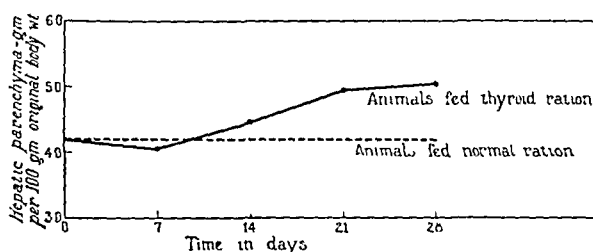


Chart 3.—Comparison of the changes in the average percentage weight of the livers of rats not operated on but fed thyroid ration with the changes in the average percentage weight of the livers of rats not operated on which were fed a normal ration.

Normal rats not operated on were also studied to determine the effect such a diet might have on the weight of the liver and the ratio of the weight of liver to the weight of body. Twenty rats, known to be healthy and of comparable strain, were isolated and fed the normal ration plus the thyroid ration in amounts similar to those fed the hepatectomized rats. The average weight of these rats was 153.8 ± 2.2 Gm. and, by means of the regression equation, the average weight of the livers was estimated to be 6.46 ± 0.09 Gm. The average per-

centage of the weight of the liver in relation to the weight of the body was 0.042. Five rats were killed each week for four weeks, and the changes in the average weight of the animals and the average weight of the livers from the estimated average weight before thyroid gland was fed were computed (table 2).

The rats not operated on lost weight as did the hepatectomized rats. After seven days of feeding with thyroid gland, an average loss of 8 Gm. was recorded; the rats killed at the end of the second week had lost 4 Gm., and those killed at the end of the fourth week had lost 2 Gm. The changes in the amount of hepatic parenchyma of rats killed after one, two, three and four weeks of being fed the thyroid ration are condensed (table 2, chart 3). The average weight of the livers of rats killed at the end of the first week was 0.109 Gm. less than that estimated before the rats were placed on the thyroid ration. Increases in the weight of the hepatic parenchyma of rats fed the desiccated thyroid ration were not marked until in the second week. No immediate or initial effects were induced. The same reaction, it will be recalled, occurred after partial hepatectomy. It was not until the fourteenth day after operation that the average weight of the livers of rats fed thyroid gland considerably exceeded that of rats fed the standard ration and operated on. The average weight of the livers of rats fed desiccated thyroid gland and not operated on increased 0.363 ± 0.59 Gm., and this rate of increase continued, so that after four weeks of the diet, the increase was greater by 1.254 ± 0.25 Gm. when the rats were fed the thyroid ration.

SUMMARY

The addition of 1 per cent, by weight, of desiccated thyroid gland to a standard ration increased the extent of the restoration of the liver following partial surgical removal. Similarly, the livers of rats not operated on, and fed the thyroid ration, increased in size after the second week, and by the fourth week were greater by 20 per cent than their estimated preexperimental weights.

Laboratory Methods and Technical Notes

AN INEXPENSIVE APPARATUS FOR ROUTINE PARAFFIN EMBEDDING IN VACUO

With Notes on the Technic of Dehydration, Clearing and Paraffin Infiltration of Tissues

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While the use of a vacuum in facilitating the infiltration of tissues with paraffin has been known at least since 1884 (Lee¹), the procedure appears to have been little employed. Its advantages in economy of time, reduction of the period of immersion of tissues in melted paraffin and superior infiltration of the tissues containing internal cavities were pointed out by Lee.

Three or four years ago I employed an extemporaneously arranged vacuum to facilitate the infiltration of pulmonary tissues with paraffin. The results were so favorable that an inexpensive apparatus for the routine use of a vacuum in paraffin embedding was devised and has been in regular use for about three years.

DESCRIPTION OF APPARATUS

The essential part of such an apparatus is a chamber in which a vacuum may be maintained at the temperature of melted paraffin. My associates and I have found satisfactory a 6 or 8 quart aluminum pressure cooker such as is sold for kitchen use for \$7 or \$8. The type having hinged lugs with winged nuts to hold the lid on is more satisfactory than the type with a compression collar.

Such pressure cookers have on the lid a safety valve, an aneroid pressure gage and a release valve. The safety valve and the pressure gage are unscrewed and removed and are replaced by screw plugs. The release valve is retained and is used for releasing the vacuum.

A pipe line to a vacuum pump must be supplied. For this purpose a hole is tapped through the side of the pressure cooker near the top, a piece of threaded pipe is passed through the hole and nuts are applied inside and outside the wall of the cooker and screwed tightly against the wall from both sides. To the outer end of the piece of iron or brass pipe a length of $\frac{1}{2}$ inch (1.2 cm.) lead pipe is attached which leads to a three-way stopcock. One of the other two openings of this stopcock leads to the upper end of a piece of heavy glass tubing 40 inches (101 cm.) long which is attached vertically to the wall of the laboratory and the lower end of which dips into a bottle of mercury. A yardstick or meter-stick

From the National Institute of Health.

1. Lee, Arthur Bolles: *The Microtome's Vade-Mecum*, ed. 7, Philadelphia, P. Blakiston's Son & Co., 1921, p. 80.

fastened to the wall beside the glass tube completes the vacuum gage. The third opening of the stopcock is attached to another length of lead pipe which leads to the vacuum pump. An ordinary 250 cc. vacuum flask of heavy glass is inserted into this line near the pump to serve as a trap for water or oil from the pump.

This vacuum chamber may be placed on its side on a small sheet metal support inside an ordinary paraffin oven or a 60 degree incubator. The pipe line to the three-way stopcock leads out through one of the holes in the side or the top of the incubator. A double shelf, furnishing two shelves for small beakers or bottles, may be inserted in the vacuum chamber.

In case a paraffin oven or a 60 degree incubator is not available, the vacuum chamber may be placed upright on a sheet metal collar in a hotel size soup stock pot which serves as a water bath. A thermostat element such as is used for gas-

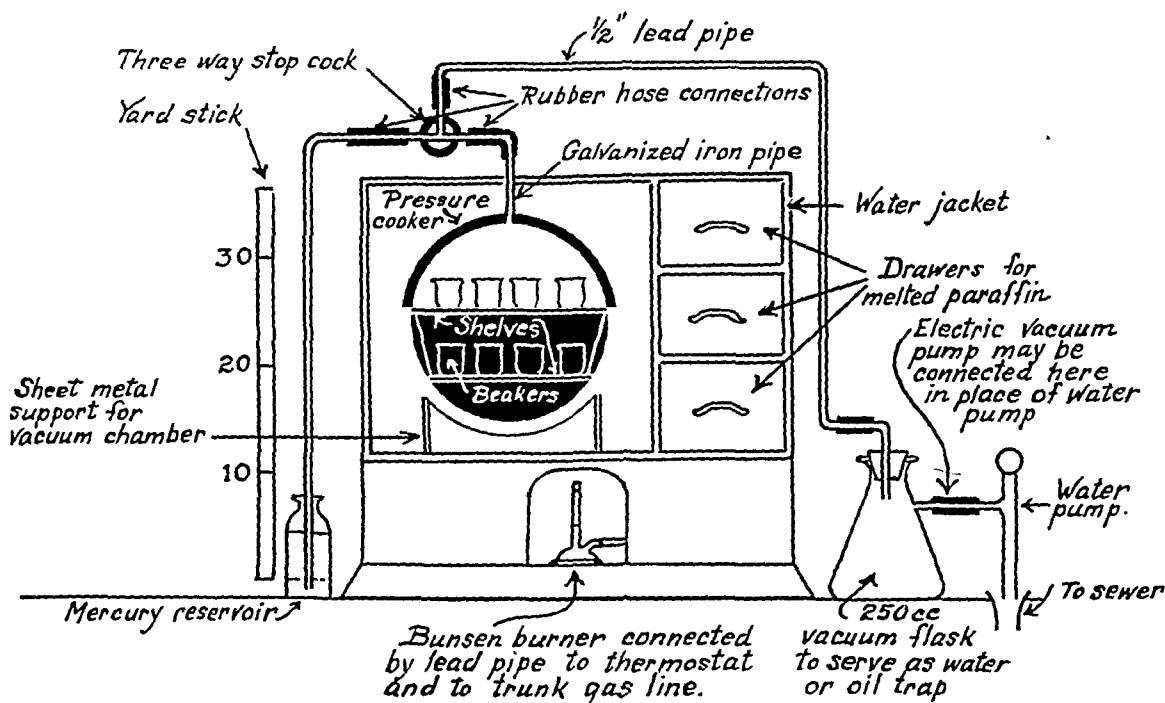


Fig. 1.—Diagram showing a pressure cooker used as a vacuum chamber and installed in an ordinary paraffin oven.

heated water baths may be inserted through a hole in the sheet metal collar beside the vacuum chamber, and the temperature may be satisfactorily regulated by this means. The trays ordinarily supplied with pressure cookers may be used as shelves and the bottom used for the stock supply of melted paraffin.

The accompanying diagrams (fig. 1 and 2) illustrate fully the two types of installation.

A pump capable of reducing the pressure inside the chamber to from 25 to 50 mm. of mercury is desirable, though pressures as high as 125 mm. may be quite satisfactory.

TECHNIC OF EMBEDDING IN PARAFFIN

The following technic permits routine embedding in from three to five hours after cutting blocks of fixed material:

Blocks from 1 to 3 mm. thick are immersed in four successive baths of acetone of from thirty to forty minutes' duration. For the last change, fresh acetone

of U. S. P. grade, costing about \$1.50 per gallon, is used. For the third change we employ the acetone which has been used once for the last change, which is then used similarly for the first two changes. The acetone used for the first change is discarded or put aside for redistillation. The final acetone bath is followed by thirty minutes in benzene or from thirty to sixty minutes in cleaner's gasoline. After this, the specimens are placed in melted paraffin in the vacuum chamber, the chamber is closed and the pump turned on until the mercury rises 28 or 29 inches (71 to 73 cm.) in the gage. The three-way stopcock is then turned so that the

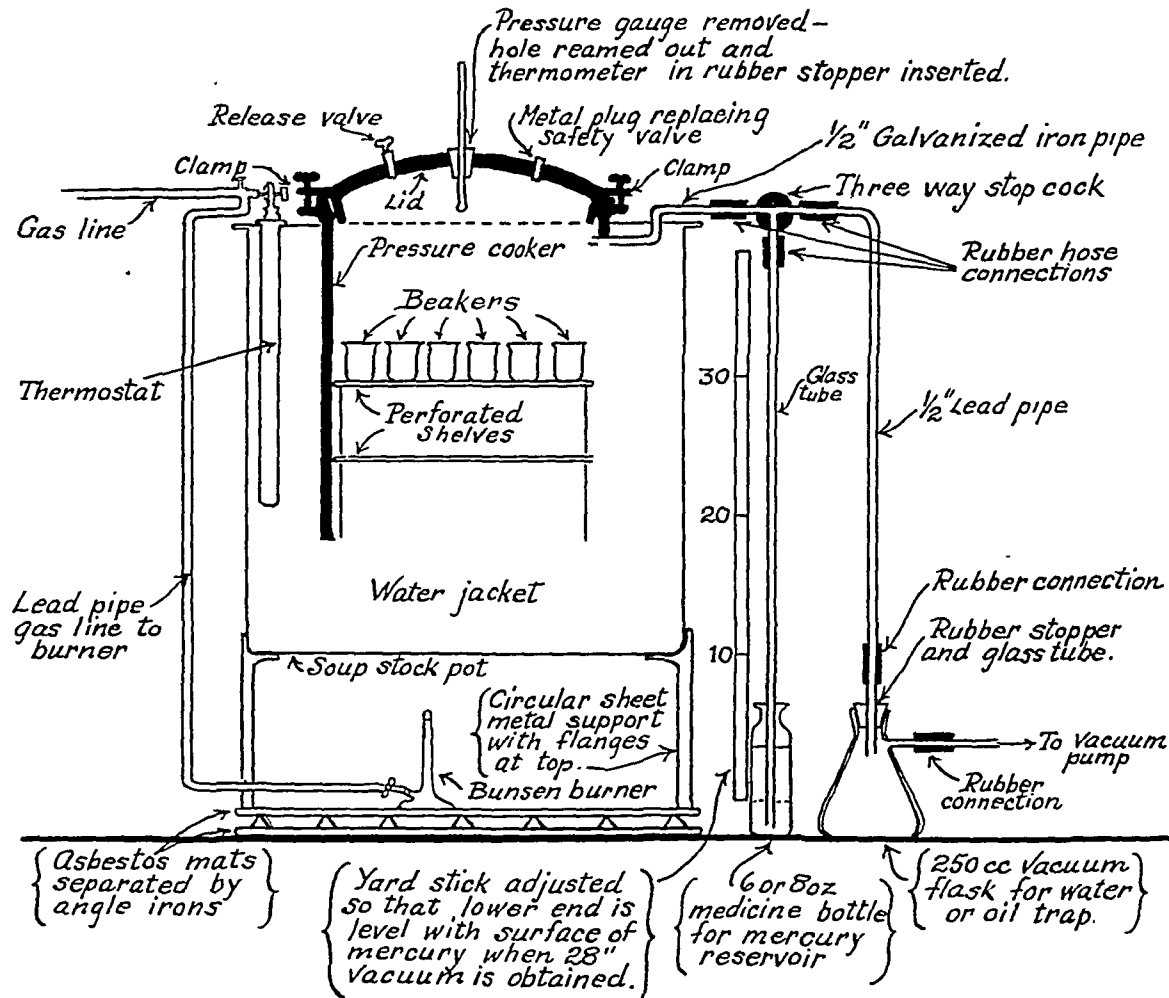


Fig. 2.—Diagram showing an improvised paraffin oven built about the kitchen type of pressure cooker and used as a vacuum chamber.

chamber remains connected with the gage but not with the pump line. Ten minutes later the release valve is opened and the vacuum released. When the objects are difficult to embed, the exhaustion of the chamber may be repeated. The chamber is then opened, and the objects are embedded as usual. Individual wire gauze covers for the specimen bottles or beakers should be provided, as the paraffin sometimes boils over and specimens may thus be lost. A square of fine-meshed copper gauze, an inch wider than the top of the bottle or beaker, folded down onto the sides of the container is a satisfactory cover. It may be cleaned by burning off the paraffin.

A volatile paraffin solvent, such as xylene, benzene, chloroform or gasoline, should be used, as nonvolatile solvents remain in the paraffin and impair its consistency. Cleaner's gasoline is the most generally satisfactory, as it hardens tissues less than any of the others. The cleaner's grade should be insisted on, as fuel gasolines commonly contain some nonvolatile oil.

This technic causes remarkably little shrinkage. The infiltration of air-containing tissues as well as of ordinary parenchymatous and fleshy tissues is excellent. Shrinkage of the tissues within the paraffin blocks after a period of storage is never seen.

For tissues containing large amounts of fat, which are notoriously difficult to section after being embedded in paraffin, we find that interposing about four successive thirty minute baths in benzene between the dehydration with acetone and the infiltration with paraffin greatly improves the consistency.

Shrinkage of the pyramidal cells in formaldehyde-fixed blocks of cerebral cortex may be avoided by incubating the blocks for twenty-four hours at 37 C. in 2.5 per cent potassium dichromate, transferring them to 50 per cent alcohol for one-half day and to 80 per cent alcohol for another half day or longer, as may be convenient, and then dehydrating, clearing and embedding as described.

Very tough tissues which are difficult to cut both in the gross and after embedding may be improved in consistency by passing them from the final acetone bath into cedar oil for over night or longer. It is then necessary to remove the cedar oil before infiltration with paraffin by immersing the blocks in two successive thirty minute baths of gasoline or benzene. Used cedar oil may be freed from acetone by putting it in a beaker in the vacuum chamber at from 57 to 58 C. and leaving it for twenty minutes in vacuo; it is then as good as fresh cedar oil for clearing.

General Review

HYPERPARATHYROIDISM (RECKLINGHAUSEN'S DISEASE OF BONE)

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NEW YORK

(Concluded from page 112)

CLINICAL FEATURES

The indications for diagnosis, on the basis of symptomatology, vary with each case.

Sex and Age.—No sex factor is indicated for this disease; the incidence of reported authentic cases seems to favor the female, but if this is so, the finding is purely accidental. Most patients seem to fall in the middle adult group (from 30 to 50 years). Cases of hyperparathyroidism have, however, been reported in children and in adults over 50 years of age.

Pain.—Study of the histories of many proved cases brings out strikingly the importance of pain as a dominant clinical feature. The pain is generally referred to the bones and joints of the lower extremities and to the spine; it is exaggerated by physical activity, although it may be present in repose. In the evolutionary stages of the disease, especially before the development of deformities or fractures, the patient may go the rounds of physicians and clinics seeking relief for what is suspected to be rheumatic pain. As the disease progresses, the pain may become so severe that the patient winces with pressure on, or compression of, the bones. Snapper's¹¹⁰ patient suffered so severely from pain that he could not bear the weight of the ordinary bed sheets. Quick and Hunsberger,¹¹¹ in giving the clinical history of their patient who suffered extreme deformity of almost the entire skeleton, noted the absence of pain; however, they mentioned pain as a distressing symptom in this patient during the earlier evolutionary stages of the disease.

Muscular Weakness and Hypotonia.—Muscular weakness and lassitude are early manifestations of the disease and are frequently associated with the pain. Difficulty in coordinating muscular movements may also be experienced. Hypotonia to a marked degree may eventually

From the Laboratory Division, Hospital for Joint Diseases.

110. Snapper, I.: Arch. Int. Med. **46**:506, 1930.

111. Quick, A. J., and Hunsberger, A.: J. A. M. A. **96**:745, 1931.

assert itself. Diminished electrical irritability of muscle and nerves occurs, possibly twice the amount of current normally required being needed to produce normal reactions. The relation of electrolytes to the contractility of tissues has long been established. After removal of the parathyroids, the low serum calcium and high serum phosphorus are associated with increased electrical excitability, hypertonia and tetany. In hyperparathyroidism, on the other hand, the increased serum calcium and decreased serum phosphorus are associated with decreased electrical excitability, with hypotonia and with muscular weakness. Hypercalcemia, produced experimentally by the injection of calcium salts, likewise results in hypotonia with a simultaneous decrease of the serum phosphorus. On the other hand, hyperphosphatemia, following the injection of phosphate, results in phosphate tetany, the serum calcium being simultaneously lowered.

Nausea, Vomiting and Constipation.—Nausea and vomiting, sometimes with severe abdominal pain, may accompany the other symptoms, especially in younger patients. When Quick and Hunsberger's¹¹¹ patient was about 22 years of age, he complained of persistent nausea. Boyd, Milgram and Stearns¹¹² reported the case of a man, aged 21, who had periodic attacks of severe abdominal pain and vomiting lasting for about three days and recurring about every three weeks for a year. Pemberton and Geddie's¹¹³ patient, a girl, aged 14, complained chiefly of vomiting, pallor and loss of weight; she had recurrent spells of vomiting (at about two week intervals, lasting from one to five days). The attacks seemed to appear without any direct cause. Ask-Upmark¹¹⁴ recorded that his patient, who died before operation, had vomited daily for two weeks before admission to the clinic. I am led to interpret such spells of nausea and vomiting as evidences of acute intoxication attributable to acute hyperparathyroidism. It is interesting, by analogy, that in experimental hyperparathyroidism the younger animals are more susceptible to parathyroid extract-Collip than the older ones. Young dogs on a normal diet, with relatively small doses of parathyroid extract, will readily evidence acute intoxication should precautions as to the dosage be relaxed.

Another relevant symptom is the occurrence of constipation; the majority of patients suffer severely from it for a great length of time.

Polydipsia, Polyuria and Urolithiasis.—Increased thirst is common, and is conditioned by the increased excretion of calcium and phosphorus through the kidneys. Since large quantities of fluid are simultaneously excreted with these salts, the thirst, in compensation, becomes pro-

112. Boyd, J. D.; Milgram, J. E., and Stearns, G.: J. A. M. A. **93**:684, 1929.

113. Pemberton, J. deJ., and Geddie, K. B.: Ann. Surg. **92**:202, 1930

114. Ask-Upmark, E.: Acta med. Scandinav. **74**:284, 1930.

nounced. Nocturia may be a distressing feature of the polyuria. Urination may be painful; some patients pass gravel. Renal stones are to be observed, roentgenologically or at autopsy, in as many as one third of the cases of Recklinghausen's disease. In experimental hyperparathyroidism, renal calculi have not appeared, although metastatic calcification of the kidneys is a common feature in acute hyperparathyroidism.

Other Manifestations of the Disease.—These vary with the individual case. Loss of appetite and loss of weight are nearly always present and may become pronounced; the patient is sometimes reduced to such a state of emaciation as to appear utterly wasted. Obvious skeletal deformities may be present; the thoracic cage is often greatly deformed because of the kyphosis and kyphoscoliosis; the extremities may be shortened, secondary to fractures and their resultant deformities. Reduction in height is the natural consequence.

When the disease appears in children, roentgenologic examination of the skeleton may disclose signs strongly suggesting late rickets rather than Recklinghausen's disease. Because of this, roentgenologists have erroneously reported cases of Recklinghausen's disease in children as showing rachitic complication. Duken's ¹¹⁵ case of Recklinghausen's disease in a girl aged 14 presented roentgenologic appearances considered typical of late rickets: a rachitic rosary, widening of the metaphyses and generalized porosis. Cessation of growth had occurred at the age of 12.

Stunting has been observed in other cases of Recklinghausen's disease, when the pathologic processes were very active before full physiologic growth had been attained. Likewise, in young dogs, experimental chronic hyperparathyroidism has led to stunted growth.^{30a} Furthermore, Bodansky, Blair and I ⁴² showed that in hyperparathyroidism in young, growing guinea-pigs such sites as the costochondral junctions and the metaphyses of long tubular bones were most predisposed to changes. The last-mentioned fact explains why in children the lesions of hyperparathyroidism occurring at the costochondral junctions and at the metaphyses should be suspected roentgenologically as being of the nature of rickets.

DIAGNOSTIC AIDS

Serum Calcium and Phosphorus.—Determination of the serum calcium and serum phosphorus is a prime requisite for diagnosis. However, too much reliance should not be placed on any one procedure for aid in determining the presence of hyperparathyroidism. Certainly, the high serum calcium values that may be observed occasionally in

115. Duken, J.: Ztschr. f. Kinderh. 46:114, 1928.

multiple myeloma or with metastatic carcinoma of bone would be misleading if considered alone in framing a diagnosis. Methods for the determination of serum calcium and phosphorus, as standardized within recent years, have given reliable figures for normal values as well as for values in pathologic conditions. Most serum calcium values for normal adults are between 10 and 11 mg. per hundred cubic centimeters, with relatively few values outside of that range. The serum phosphorus in normal adults may be stated to be about 3 mg. per hundred cubic centimeters.

In clinical hyperparathyroidism, varying degrees of hypercalcemia and hypophosphatemia have been observed. Serum calcium values as high as 23.6 mg. and serum phosphorus values as low as 1.1 mg. per hundred cubic centimeters have been reported. On the other hand, in some cases the serum calcium value may not be consistently high. Wilder¹¹⁶ reported a case in which most values were within normal range; the higher values (among which 13.2 mg. was the highest) were observed during the period of a diet high in vitamin D and ultraviolet irradiation. The serum calcium values obtained for any patient may fluctuate considerably over a long period.

However, an elevated level of the serum calcium and a depressed level of the serum phosphorus may not necessarily be present, as in a more recent case which Wilder and his associates¹¹⁷ described. Their patient, a woman of 48 years, had changes in the bones which roentgenographically suggested Recklinghausen's disease, but because the serum calcium and phosphorus values were within normal limits a diagnosis of hyperparathyroidism was not made. At a subsequent examination, nineteen months later, additional roentgenograms showed further progress of the disease, but the values of serum calcium on successive days were 11.5, 11, 10.6 and 11 mg. per hundred cubic centimeters; those of phosphorus were 2.9, 3, 2.7 and 2.3 mg. Since a definite negative balance for calcium was present, it was decided to explore the neck, and a parathyroid adenoma was removed. Bodansky and I^{31b} have shown that even hypocalcemia may develop in young dogs suffering from chronic hyperparathyroidism if they are maintained on a diet low in calcium; this hypocalcemia may be associated with tetany.

The existence of a nephritic complication associated with uremia may still further confuse the evaluation of the estimations of serum calcium and serum phosphorus in Recklinghausen's disease. It is well known that the serum phosphorus level is elevated and the serum calcium level is depressed to a very low figure in uremia. When uremia compli-

116. Wilder, R. M.: *Endocrinology* **13**:231, 1929.

117. Wilder, R. M.; Camp, J. D.; Robertson, H. E., and Adams, M.: *Proc. Staff Meet., Mayo Clin.* **7**:597, 1932.

cates Recklinghausen's disease—and it may, because of the great frequency of urolithiasis and associated renal infection—the urea nitrogen level becomes greatly elevated as does that of the serum phosphorus, and the serum calcium (which in the absence of the uremia may have been increased) is decreased and reaches normal or subnormal levels.

It is surprising that the ingestion of large quantities of calcium by patients with clinical hyperparathyroidism has little effect on the serum calcium and phosphorus. Thus, the danger of hypercalcemia and hyperphosphatemia during short periods of excessive ingestion of calcium, seems not to prevail. Bauer, Albright and Aub¹¹⁸ found that during one period when their patient received 9.14 Gm. of calcium and the balance was + 5.02 Gm., the serum calcium was 14 mg. per hundred cubic centimeters and the serum phosphorus 1.7 mg.; during a period with an intake of 0.29 Gm. of calcium and a balance of — 0.95 Gm., the serum calcium was 13.7 mg. and the phosphorus 1.9 mg.

Mineral Metabolism.—Study of the calcium and phosphorus balances constitutes a most important diagnostic chemical procedure to be followed in this disease. A complete study of mineral balance requires so much careful attention to numerous details that in most institutions it is difficult, if not impossible, to carry out such a procedure. Directions for carrying on such studies may be found in the recent papers of Bauer, Albright and Aub,¹¹⁹ Bassett, Elden and McCann¹²⁰ and Salter, Fulton and Angier.¹²¹ Of the two excretions, measurement of the calcium is by far the more important, as excessive excretion of calcium in the urine is regularly found in active cases. Normally, the urinary excretion of calcium is relatively small and is not materially increased by a high calcium intake. Even intravenous administration of calcium may have little influence on urinary excretion. Thus, in normal persons the great differences in output, resulting from variation in calcium intake, occur chiefly in the stool. As Hannon, Shorr, McClellan and DuBois²⁸ pointed out, in normal persons from 70 to 90 per cent of the calcium is excreted in the feces and from 10 to 30 per cent in the urine; in those with hyperparathyroidism from 10 to 30 per cent is excreted in the feces and from 70 to 90 per cent in the urine.

In the studies of calcium balance, it seems preferable, as Bauer, Albright and Aub¹¹⁹ pointed out, to compare the excretion of calcium in normal persons on a diet low in calcium (standardized as to the

118. Bauer, W.; Albright, F., and Aub, J. C.: J. Clin. Investigation 8:229, 1930.

119. Bauer, W.; Albright, F., and Aub, J. C.: J. Clin. Investigation 7:75, 1929.

120. Bassett, S. H.; Elden, C. A., and McCann, W. S.: J. Nutrition 4:235, 1931.

121. Salter, W. T.; Fulton, C., and Angier, F.: J. Nutrition 4:1, 1931.

ingredients of the diet and its acid-base equivalents). Thus, many variables which influence calcium absorption are avoided; even such factors as age, sex and nitrogen balance have to be considered before accurate comparisons can be made. Two of the three patients studied by Bulger, Dixon and Barr¹²² had excessive fecal excretion of calcium, while all three showed excessive urinary excretion of calcium. The patient of Hannon, Shorr, McClellan and DuBois was in negative calcium balance on an intake of 0.5 Gm. a day; 0.7 Gm. daily was necessary to maintain him in equilibrium. A low fecal excretion of calcium, in view of a satisfactory intake, indicated good absorption from the intestine. On extremely high calcium intakes, several grams or more a day, a negative balance may be converted to a positive one; this has been the finding on short periods of study. It is my belief that such positive balances cannot be maintained in active cases of hyperparathyroidism; it is quite certain that clinical hyperparathyroidism is not to be permanently corrected by increasing the calcium intake.

Studies of calcium balance in hyperparathyroidism may be tremendously simplified by determining only the calcium excreted in the urine; as already stated, in hyperparathyroidism most of the calcium is excreted through the urine (as opposed to the excretion of calcium chiefly through the feces, normally). A convincing illustration of a negative calcium balance in generalized osteitis fibrosa cystica by such means was given by Snapper.¹¹⁰ He employed a diet on which normal persons in control experiments excreted from 30 to 100 mg. of calcium daily in the urine. His patient with hyperparathyroidism excreted about 400 mg. of calcium before operation and about 25 mg. immediately after operation.

There is, however, less consistency in the results of the studies of phosphorus balance. For instance, a case of hyperparathyroidism studied by Hannon, Shorr, McClellan and DuBois,²⁸ in which a diet relatively high in calcium was given, showed conflicting results regarding the phosphorus balance; in five of the periods the balance was positive, while in the two final periods the balance was negative. The same patient, on a diet low in calcium, studied by Bauer, Albright and Aub,¹¹⁸ showed consistent loss of phosphorus coincident with loss of calcium. An unusually high proportion of the phosphorus was excreted in the urine, and the loss of phosphorus was in close agreement with the loss of calcium. The same patient, when again observed by McClellan and Hannon¹²³ (a few months after the removal of two normal parathyroid glands at the Massachusetts General Hospital), showed that a positive phosphorus balance was maintained throughout the entire period of

122. Bulger, H. A.; Dixon, H. H., and Barr, D. P.: *J. Clin. Investigation* 9:143, 1930.

123. McClellan, W. S., and Hannon, R. R.: *J. Clin. Investigation* 8:249, 1930.

observation, even in those periods when there was definite loss of calcium from the body.

It must, however, be noted that a negative calcium and phosphorus balance is not a finding narrowly specific for hyperparathyroidism. For instance, in osteomalacia, there is, as Miles and Feng¹²⁴ showed, a negative balance for these substances. Nevertheless, the excessive loss of calcium and phosphorus is by way of the feces. Thus, the urinary excretion of calcium in this disease, unlike that in hyperparathyroidism, is diminished.

While it is true that studies of mineral balance are valuable in diagnosing Recklinghausen's disease, one must consider the handicaps which studies of short periods (as practiced at the present time) must of necessity introduce. It should be remembered that these studies of mineral balance as carried out currently can reflect in only the grossest manner the circumstances concerning the deposition or resorption of calcium and phosphorus with regard to the bones. That the present methods of testing for the loss of calcium and phosphorus from the skeleton are too inexact when the loss of these substances proceeds relatively slowly may be surmised from the work of Aub and Farquharson.¹²⁵ They had under observation cases in which there was great destruction and loss of bony substance (extensive metastatic carcinomatous nodules in the bones and advanced multiple myeloma), but the excretion of calcium and phosphorus in both the urine and the feces was within normal range for adults on a diet low in calcium during the periods studied.

Serum Phosphatase.—Phosphatase is an enzyme present in practically all the tissues of the body; it is found in large quantities in the intestinal mucosa, kidneys, leukocytes, cartilage undergoing endochondral ossification and connective tissue in which bone formation is in progress. This enzyme has the capacity for splitting organic phosphorus compounds and liberating inorganic phosphorus; at the same time, it possesses the ability to synthesize organic phosphorus compounds and to utilize inorganic phosphorus. Normally, phosphatase is present in small amounts in both the serum and the plasma of the blood. Larger amounts exist in the blood of infants and children than in that of adults. Kay,¹²⁶ who first systematically studied plasma phosphatase in a number of disorders, observed that it was abnormally increased in the plasma in some cases in which bone lesions were present (Paget's disease, active rickets, Recklinghausen's disease, etc.). Bodansky,¹²⁷ in this laboratory,

124. Miles, L. M., and Feng, C. T.: J. Exper. Med. **41**:137, 1925.

125. Aub, J. C., and Farquharson, R. F.: J. Clin. Investigation **11**:235, 1932.

126. Kay, H. D.: J. Biol. Chem. **89**:249, 1930.

127. Bodansky, A.: J. Biol. Chem. **101**:93, 1933.

developed a method for the determination of serum phosphatase which is free from a number of theoretical and practical objections which have been raised in regard to Kay's method. The values obtained by Bodansky's method, which are based on a large series of determinations, are estimated in units per hundred cubic centimeters of serum; normal children show from 5 to 12 units, and normal adults from 1.5 to 4 units. In a case of advanced Recklinghausen's disease the serum phosphatase value which Bodansky determined by his method was 20 units. Following the removal of a parathyroid adenoma, it dropped to about 10 units after a few months. It is extraordinary that the elevation of the serum phosphatase values in advanced cases of Recklinghausen's disease is nowise comparable to the extreme elevation of such values in cases of florid rickets or of disseminated florid Paget's disease. In this laboratory, values of 100 units or more were found in some active instances of the two last-mentioned conditions.

An analysis of the serum phosphatase values in many conditions in which bones were obviously affected (as obtained in this laboratory) has prompted the formulation of a particular conception of the mechanism underlying elevation of the level of the serum phosphate. This has been prepared for publication.¹²⁸

Roentgenographic Aids in Diagnosis.—It is hardly necessary here to give a detailed discussion of the roentgenographic changes as they affect the skeleton; such details may be found in the articles of Dresser and Hampton,¹²⁹ Camp¹³⁰ and Kienböck and Markovits.¹³¹ The disease is insidious in its development, evolving over a period of years and reaching advanced stages more rapidly in some patients than in others. Since patients may be examined in early or late stages, it is evident that the roentgenographic appearances may be quite different in any number of given cases. Since clinical diagnosis is now being made earlier, the advanced roentgenographic appearance of this disease (in which cysts and giant cell tumors may be seen) is less frequently encountered. However, no matter what the stage of the disease, the changes are more or less constant in one direction; that is, there is progressive thinning of the bones.

The roentgenologist, therefore, in interpreting roentgenograms showing generalized osteoporosis, should bear in mind the possibility that he is dealing with an early stage of Recklinghausen's disease. It must be promptly brought to attention that Recklinghausen's disease is

128. Bodansky, A., and Jaffe, H. L.: *J. Clin. Investigation*, to be published.

129. Dresser, R., and Hampton, A. O.: *Am. J. Roentgenol.* **25**:739, 1931.

130. Camp, J. D.: *J. A. M. A.* **99**:1913, 1932.

131. Kienböck, R., and Markovits, E.: *Fortschr. a. d. Geb. d. Röntgenstrahlen* **41**:904, 1930.

extremely rare. When a case in which generalized osteoporosis is present is suspected of being one of hyperparathyroidism, the final task of making the diagnosis must be given to the clinician and the clinical laboratory. The roentgenologist can safely make a diagnosis of Recklinghausen's disease only when the lesions in the bones are fairly advanced, and generalized osteoporosis, with cysts, giant cell tumors, fractures and a granular mottled appearance, is demonstrable in a few or in many bones.

Camp,¹³⁰ like others, recently stressed the miliary mottling and granular appearance of bones with advanced changes caused by hyperparathyroidism. This roentgenographic appearance was most prominently observed in the flat bones, especially the calvarium. He laid much stress on the presence of this granular mottling in making a diagnosis of Recklinghausen's disease. On pathologic grounds it is quite evident that the granular, mottled shadow cast by a bone changed by hyperparathyroidism is caused by a large quantity of new bone (consisting of thin, closely set, partially calcified trabeculae) which has replaced the original bone. Therefore, unless the resorption of the original bone has progressed to an advanced degree, and numerous newly formed trabeculae have appeared in the connective tissue which replaced the original bone, no granular, mottled shadow will be cast. For instance, in a long tubular bone, the progress of the lesions will be as follows: The original trabeculae become indistinct, and the cortical bone thins, so that a more or less homogeneous porotic shadow is cast before any semblance of a mottled, granular appearance occurs. Thus, while in any given case the appearance may be as Camp described it, the granular, mottled appearance applies only to bone that is in a certain pathologic stage.

The roentgen appearances of the skull may vary considerably in different cases. Visible deformities in contour may exist; softening of the bones at the base may cause flattening and diminution in the depth of the posterior fossa. The calvarium, however, presents the widest variations; it may be thinned and even have bony defects, a result of the osteoporosis. On the other hand, the calvarium may be thickened, either generally or irregularly. Irregular thickening is most often confined to the frontal, temporal or parietal regions. The details concerning the pathologic appearance of such a thickened area have been discussed; roentgenographically, the thickened portion of the calvarium shows the finely mottled, granular texture. The rest of the skull, including the facial bones, usually shows generalized osteoporosis; cysts and giant cell tumors may be observed in the mandible and maxillae.

The spine, as indicated in the description of the pathologic changes, may show marked deformities which are plainly evident roentgenographically.

Long tubular bones show progressive cortical thinning; expansion of the medullary cavity may appear. Cysts and giant cell tumors are sharply delineated, and may be surrounded by shells of bone. They have been observed even in the metatarsal and metacarpal bones. Infractures are frequently observed roentgenographically. Fractures (which are common) tend to unite readily, but excess callus is not seen. A cyst which has been the site of a fracture may show spontaneous healing. In advanced cases, the phalanges may show cortical resorption and even pathologic fractures. In children, many rachitic-like features may appear, such as bowing of the bones and slipping of the epiphyses. Roentgenographically, the metaphyses of the long tubular bones may be widened,¹¹⁵ suggesting late rickets.

In view of the present status of the knowledge of Paget's disease, osteomalacia and senile osteoporosis, the diagnostic problems with which the roentgenologist has been confronted in regard to Recklinghausen's disease can, to a great degree, be put at rest. The differentiation between it and Paget's disease (especially as regards the long tubular bones) has been plain to many roentgenologists. Confusion between these diseases has occasionally arisen because of the relatively frequent thickening of the skull in Recklinghausen's disease. However, when the thickening of the skull is considered in conjunction with the rest of the bony changes there should be no confusion whatever between Recklinghausen's and Paget's disease. Most often, confusion has arisen between osteomalacia and Recklinghausen's disease, and this is sometimes pardonable. Osteomalacia, it should be remembered, does not have giant cell tumors and cysts—which may be present in Recklinghausen's disease. Furthermore, the resorption of the original bone is often not as pronounced in osteomalacia as it is in an advanced case of Recklinghausen's disease. Too much reliance should not be placed on deformity of the pelvis, for in advanced cases of this disease, the pelvis may be as badly deformed as in genuine osteomalacia.

DIFFERENTIATION FROM OTHER MALACIC DISEASES

The differentiation of Recklinghausen's disease from other malacic diseases has been greatly clarified in recent years, as a result of much progress in the comprehension of disturbances of mineral metabolism. There is therefore no need for discussing at great length the means of distinguishing the other generalized diseases of bone from this one.

Osteomalacia.—The condition with which Recklinghausen's disease has most often been confused is genuine osteomalacia. This perplexity

was rife before 1891,¹ and persisted for many years thereafter. Several enlightening considerations have contributed toward separating these diseases. The most important are: the proof that a deficiency of vitamin D is operative in the production of osteomalacia; the finding that Recklinghausen's disease is caused by hyperparathyroidism; the recognition that despite the apparent clinical similarity pathologic differences exist to differentiate these diseases. On microscopic grounds, the wide osteoid borders on the trabeculae, the absence of considerable fibrous tissue replacing the bone, the relatively infrequent presence of osteoclasts and the presence of a congested lymphoid marrow distinguish osteomalacia from Recklinghausen's disease. All these features have been discussed at length in the introductory and pathologic sections. It was pointed out that the cases described in the older literature as examples of osteomalacia with cysts and giant cell tumors are undoubtedly instances of Recklinghausen's disease.

In the United States, up to the present time, osteomalacia in its advanced form has been extremely rare; its incidence is 'probably' even less than that of clinical hyperparathyroidism. Miles and Feng,¹²⁴ who studied the blood of osteomalacic patients (Chinese), whose illnesses had existed from less than one year to twenty years, found that in these cases there was considerable reduction in the serum calcium (5 to 7.4 mg. per hundred cubic centimeters); the serum phosphorus was from 1.8 to 3.8 mg. per hundred cubic centimeters. These investigators made metabolic studies of patients on a diet low in calcium, and found a negative calcium balance. Gargill, Gilligan and Blumgart¹³² studied a case of osteomalacia at Boston, and also observed that on a diet low in calcium there was a negative calcium metabolism. This persisted even when the calcium ingested was excessive. Miles and Feng corrected the negative calcium balances in their patients merely by the administration of cod liver oil. Gargill, Gilligan and Blumgart found that their patient would not store calcium and phosphorus (indicative of healing) until they administered as large quantities as 100 cc. of cod liver oil concentrate daily.

While the condition of the parathyroid glands may be completely normal in osteomalacia (which is never the case in Recklinghausen's disease), occasionally slight enlargement of all the parathyroids may be encountered, while even more infrequently one of these glands may reach a fairly large size. Parathyroid enlargement in osteomalacia must be looked on as secondary to the bone disease and therefore compensatory. Erdheim¹³ contended that even when the parathyroids are

132. Gargill, S. L.; Gilligan, D. R., and Blumgart, H. L.: *Arch. Int. Med.* 45:879, 1930.

not grossly enlarged, microscopic evidences of hyperplasia can be ascertained by special methods of histologic examination.

There need be no confusion of Recklinghausen's disease with genuine infantile rickets. However, in adolescent children, Recklinghausen's disease may produce bowing deformities of the lower extremities with widening of the metaphyses; these may be observed roentgenographically. This would introduce some possibility of mistaking this disease on clinical grounds for adolescent rickets. The parathyroids themselves are not enlarged in most cases of infantile or of late rickets.¹³³

Paget's Disease.—The distinction between Recklinghausen's disease and Paget's disease has already been well covered. Christeller's⁵¹ concept that the former is the "hypostotic," and the latter the "hyperostotic," form of fibrous osteodystrophy is now completely dissipated. Recklinghausen's disease is a generalized condition, and this feature is further opposed to the localized (although polyostotic and progressive) character of Paget's disease. The participation of the periosteum in the production of the pathologic lesions of Paget's disease is in contrast to the lack of periosteal activity in hyperparathyroidism. Lamellation of the cortex of long tubular bones of the type seen in florid cases of Paget's disease does not occur in Recklinghausen's disease, in which the cortex is thinned. The general character of the bony thickening and deformity observed in Paget's disease is not seen in Recklinghausen's disease. Giant cell tumors of the nature observed in Recklinghausen's disease do not occur in Paget's disease. The parathyroid glands lack the tumorous enlargement that is seen in Recklinghausen's disease. If the parathyroid glands are at all enlarged, the enlargement is slight, generalized and of a secondary, compensatory nature. The clinical examinations of the blood have shown no particular abnormalities in Paget's disease; furthermore, studies of mineral balance have given no constant results. In a recent summary, I¹³⁴ have detailed the anatomic and clinical features of Paget's disease which distinguish it from Recklinghausen's disease.

Generalized Osteoporosis: Senile Osteoporosis.—I wish to make clear that the so-called "inactivity atrophy or osteoporosis" and "hunger osteopathy or osteoporosis" are entirely excluded from consideration here. Furthermore, the osteoporoses secondary to endocrinous disturbances (hyperthyroidism, obesity associated with basophilic pituitary adenoma, etc.) are also excluded from this discussion. This leaves a large group of cases (senile osteoporosis) in which such pronounced rarefaction of the skeleton may occasionally occur that roentgenographic

133. Schmorl, G.: München. med. Wchnschr. **54**:494, 1907.

134. Jaffe, H. L.: Arch. Path. **15**:83, 1933.

study of the bones may suggest the presence of Recklinghausen's disease. Such bones are very transparent to roentgen rays, are brittle and may fracture.

The conditions operating to produce this type of osteoporosis are related to the general involutionary process that occurs in all aging and senile persons. Senile osteoporosis has been studied particularly by the older pathologists. Pommer's⁵⁶ concept that in senile persons physiologic deposition of new bone is decreased while physiologic resorption continues at a normal pace, so that over a period of years progressive thinning of the bones occurs, is the view that generally prevails as to the pathogenesis.

It is well known that in aged persons senile osteoporosis of the neck of the femur is the reason for its frequent fracture. In such cases, fibrous transformation of the bone, limited to the site of fracture, may be observed. Involvement of the spine, particularly the vertebral bodies, leads to kyphosis and sometimes even to greater deformities. Owing to weakening of the bony structure of the bodies, expansion of the intervertebral disks is common. With expansion of the intervertebral disks, collapse of the internal architecture of some of the bodies (which are reduced in their superior-inferior dimensions) results in proliferation of new bone in the proliferated osteogenic connective tissue. Otherwise, marrow fibrosis and new bone formation are not a part of the uncomplicated pathologic changes in senile osteoporosis.

In other words, the pure lesion is simply a chronic fatty atrophy of the bone; the trabeculae and cortex are thinned; the marrow cavity of the tubular bone increases in size; the canals of the blood vessels of the cortex are widened; the periosteal surface of the cortex is smooth; microscopic lacunar resorption is negligible; osteoid borders are not demonstrable; the fat in the marrow cavities is soft and oily. If fibrous transformation of the marrow occurs, associated with the appearance of connective tissue new bone in the fibrosed marrow, it is localized in areas in which there has been collapse of the spongy bone.

Pain from pressure on the bones is usually absent in senile osteoporosis, but in very pronounced cases it may be found: in such cases the condition has progressed to such a serious state that advanced thoracic deformities exist, which may be combined with curvature of the lower extremities and which, clinically, may produce a picture suggestive of Paget's disease. Aside from the clinical suggestion, these diseases are not in the least related.

On histologic grounds, senile osteoporosis is to be distinguished from osteomalacia and Recklinghausen's disease because there are no osteoid borders, giant cell tumors, marked lacunar erosions or the type of cysts seen in Recklinghausen's disease. In the long tubular bones of such

patients more or less large brown areas, containing hemosiderin, are occasionally seen and are referable to recent hemorrhage. Microscopically, however, accumulations of giant cells are not observed in such areas. Thus, there are no genuine brown tumors in an osteoporosis which is not caused by hyperparathyroidism. In advanced cases of senile osteoporosis, small, single and confluent cysts may be observed in some of the long tubular bones; these are nothing more than oily cysts due to liquefaction of the fatty marrow. The walls of such cysts consist of connective tissue, surrounded by normal or somewhat modified fat cells. These cysts are well illustrated in the cases of Gerth¹³⁵ and Schupp.⁴⁰ Such advanced stages of senile osteoporosis are indeed rare.

The parathyroid glands play no part in the pathogenesis of this condition; when studied, they were often found to be normal. They have occasionally been reported as showing enlargement, recognized by the naked eye. At such times, they are dark red or brownish; if the enlargement is not actual, it may be considered to be relative to the atrophy of the other organs and tissues. Maresch¹⁸ observed a case of senile osteoporosis in which one gland measured 12 by 8 by 6 mm., and which microscopically showed foci of hyperplastic proliferation.

"Fibrocystic Disease" of Problematic Origin.—It seems eminently desirable at this point to review several reported cases which, in my opinion, constitute a doubtful group; these are open to confusion with either Recklinghausen's or Paget's disease. One such case was recently described by Bradfield.¹³⁶ The patient first came under observation in 1913 at the age of 6 years; at that time he suffered from a fracture of the right femur. The disease progressed in the lower extremities between the ages of 6 and 9, and several fractures occurred in the femora and tibias; it was still active in the right humerus at the age of 18. At the time of the report it was believed that the disease was no longer active, although the major skeletal changes did not seem to be correcting themselves. On roentgenographic study, the skull was suggestive of Paget's disease, while the long tubular bones appeared thin and cystic. In 1921, a fragment of the right femur was removed and studied histologically; it showed the presence of considerable cartilage; no gross cysts or giant cell tumors were observed. At no time did any clinicopathologic investigations throw light on the etiology of the condition. Elmslie,¹³⁷ who had reported the clinical aspects of this case in 1914, also examined the biopsy slides from the specimen obtained in 1921; he confirmed the histologic findings reported by Bradfield. He further stated, in a concluding note to Bradfield's paper, that he had recently studied another case in

135. Gerth: Virchows Arch. f. path. Anat. **277**:311, 1930.

136. Bradfield, E. W. C.: Brit. J. Surg. **19**:192, 1931.

137. Elmslie, R. C.: Brit. J. Surg. **2**:17, 1914.

which the pathologic picture was similar to that alluded to; no parathyroid tumor was found on surgical exploration of the neck, and the serum calcium and phosphorus values were within the normal range.

Hirsch¹³⁸ had previously discussed another example of this condition (in many ways completely duplicating the one detailed by Bradfield). The patient was first seen in 1912, at the age of 15. The salient features of the recorded history are as follows: A slight protuberance was noted over the right parietal bone at the age of 8; another soon developed in the left cheek; the size of the head increased (from the age of 8); curvature of the spine developed early. Between 18 and 27, fracture of the clavicle and fractures of the ribs occurred; at 23, the right femur fractured. In spite of this record, in 1929 when Hirsch made his report, the patient's general health was good; the serum calcium was 10.9 mg. and the serum phosphorus 4.2 mg. Thus, during the fifteen years of observation by Hirsch, the roentgenographic lesions in the long bones showed no striking changes from their original appearance, while those in the metacarpal and phalangeal bones showed a tendency toward healing. The skull, since the inception of the lesions at 8 years, had shown a progression of the changes in the direction of Paget's disease.

Still another case of a generalized disease of bone (that Willich¹³⁹ described as an instance of "spontaneous healing in a generalized osteodystrophy") probably falls into this category. Thirty years previous to his report, the disease was ushered in with swelling of the jaw and pain in the tibia. By 1912, all the roentgenographic appearances were considered those of a generalized osteitis fibrosa; between 1912 and 1928, all the bones, with the exception of the skull, had shown considerable spontaneous regression of the lesions. In spite of all this, the skull, which shows changes like those in Paget's disease, has been increasing in size during the last few years.

Telford¹⁴⁰ also recently reported an instance of what seems to be a local manifestation of the same condition (the pathologic lesions are apparently localized in the bones of the left lower extremity). The patient, a woman 34 years of age, was well until 14, when the left femur fractured. Several years before the report, swelling of the left lower extremity with enlargement of some of the bones appeared. Histologic sections of a biopsy specimen evidenced the presence of large amounts of hyaline cartilage; this was likewise the feature in the specimen in Bradfield's case.

138. Hirsch, I. S.: *Radiology* **12**:505; **13**:44, 1929.

139. Willich, C. T.: *Beitr. z. klin. Chir.* **146**:103, 1929.

140. Telford, A. D.: *Brit. J. Surg.* **18**:409, 1931.

My impression is that these conditions are neither Recklinghausen's nor Paget's disease, and that they constitute a still unidentified entity. I strongly suspect that they have a congenital basis.

Renal Rickets.—Renal rickets, while not offering any real difficulties in differential diagnosis from Recklinghausen's disease, is a condition that probably results from a disturbance in the metabolism of calcium and phosphorus (for which the underlying chronic nephritis is evidently responsible). While albuminuria, associated with deformities of the extremities in children, has been known for a long time, the dependence of the changes in the bones on the renal disease was stressed in 1911 by Fletcher.¹⁴¹ Fishberg¹⁴² thinks that the changes in the bones may be attributed to the fact that, associated with renal disease in general, there are chronic acidosis and a diminished ability on the part of the kidney to form ammonia; in consequence of an inadequate formation of ammonia, the organism is forced to excrete fixed base. This is mobilized from the bones, and to this he refers the pathogenesis of the bony lesions of renal rickets. The recent observation by Boyd¹⁴³ seems to be in harmony with this conception. He reported an instance of rachitic-like lesions developing in a child of 10 years (subsequent to transplantation of the ureters into the rectum). Chronic acidosis developed, and this was associated with roentgenographic appearances suggestive of rickets. The changes in the bone were corrected by the daily administration of large doses of sodium bicarbonate; they were therefore the result of an acidosis, but since the acidosis could be corrected, the lesions healed.

In this connection, it may be interesting to note the observation made by MacCallum¹⁷ in 1905; at autopsy on a young patient with chronic nephritis he found a parathyroid tumor about 2 cm. in diameter; the bones were not studied. It is quite likely that the enlarged parathyroid was the result of a compensatory hypertrophy. Bergstrand³⁸ more recently has noted that resorption of bone occurs in some cases of chronic nephritis. The ribs of a subject, 17 years of age, who died of chronic glomerulonephritis, showed considerable lacunar resorption; a man, aged 58, who died of chronic glomerulonephritis, had advanced lacunar resorption of the femoral diaphysis and a bean-sized parathyroid adenoma. In regard to parathyroid enlargement in chronic nephritis, Bergstrand¹⁵ stated on another occasion that about 10 per cent of the cases may show secondary parathyroid hyperplasia.

Certain Local Lesions: Their Relation to Recklinghausen's Disease.—Consideration is here given to certain local lesions, such as solitary

141. Fletcher, H. M.: Proc. Roy. Soc. Med. (Sect. Child. Dis.) **4**:95, 1910-1911.

142. Fishberg, A. M.: Nephritis and Hypertension, Philadelphia, Lea & Febiger, 1931, p. 417.

143. Boyd, J. D.: Am. J. Dis. Child. **42**:366, 1931.

giant cell tumors, single unilocular or multilocular cysts and the various forms of so-called localized osteitis fibrosa cystica.

Solitary giant cell tumors most frequently appear in the epiphyses of tubular bones (especially the long tubular ones), although they may be observed in flat bones, in the vertebrae and even in the diaphyses or beneath the periosteum of tubular bones. These tumors, which consist of a very vascular spindle cell stroma and varying numbers of multinucleated giant cells (osteoclast type), in many respects histologically resemble the giant cell tumors of Recklinghausen's disease. Localized giant cell tumors may extend to beneath the articular cartilage and may then destroy portions of the bony end-plate; by confluence of foci, the entire bony end-plate may be destroyed; sometimes foci enter the articular cartilage. I have observed such tumors breaking into a joint. However, as was pointed out in the pathologic section, I believe them to be true blastomas and therefore not analogous to the giant cell masses of Recklinghausen's disease.

Single unilocular or multilocular cysts generally occur in the metaphyses of the long tubular bones of very young children, but may also extend into the epiphyses of such bones. Cartilaginous proliferations are occasionally observed in such cysts, but these have no connection with the original epiphyseal cartilage plate. The significance of such cartilaginous proliferations is unknown; whether they should be interpreted as callus formations or as displaced cartilaginous nests (which occur normally in the head of the femur) remains to be decided. Larger cartilaginous masses undergo cystic degeneration; this led Virchow to consider such cysts the end-results of degeneration of enchondromas. The presence of large masses of degenerating cartilage is rather the exception than the rule in simple benign cysts of bone. These localized cysts constitute a distinctive group, also not to be confused with the cysts of Recklinghausen's disease.

The various forms of so-called localized osteitis fibrosa cystica may be nothing more than delayed or otherwise abnormal and perverted healing processes (secondary to infection or trauma) or part of a healing reaction in a giant cell tumor or cyst.

Particular emphasis should be laid on the fact that no matter how closely the gross and histologic appearances of these lesions approach certain of the pathologic aspects of Recklinghausen's disease, they are in no way to be considered etiologically or pathogenically identical. Furthermore, while cystic degeneration of giant cell masses may occur in Recklinghausen's disease, there is absolutely no reason for considering solitary unilocular or multilocular cysts as the end-result or the healing stage of solitary giant cell tumor—the conception popularized in this

country by Geschickter and Copeland.¹⁴⁴ The serum calcium and phosphorus values are always within normal range in these conditions, as is the serum phosphatase, and those who have studied the mineral metabolism (for calcium and phosphorus) have also found no deviation from the normal. These conditions are not associated with tumorous hypertrophy of the parathyroid glands, and removal of normal parathyroid tissue does not alleviate them, if additional local procedures are not instituted.

When a patient presents what appear to be multiple, benign, giant cell tumors, there is always the possibility that the condition is Recklinghausen's disease. This is borne out by the report of an instance of multiple giant cell tumor made by Alexander and Crawford¹⁴⁵ in 1927; it was subsequently reported as one of proved hyperparathyroidism.¹¹¹ Even today, the danger exists of treating some of the aspects of Recklinghausen's disease as purely local disturbances. Recently, a case was reported in which the femur of a young woman was amputated because of the persistence of nonunion (for five months after a fracture). The fracture occurred through a cystic lesion, the nature of which was at first unconnected with Recklinghausen's disease. Two months after amputation, roentgenographic examination of all the long bones disclosed a generalized disease, and at operation a parathyroid tumor was removed.¹⁴⁶

TREATMENT

Parathyroidectomy: Results.—Beginning with Mandl,²⁴ it was shown that whenever a clearcut case of hyperparathyroidism had been diagnosed removal of one or more parathyroid adenomas usually resulted in immediate marked clinical improvement. Relief from pain has been one of the most striking postoperative effects; some of the patients were bedridden, but became ambulatory soon after operation. In many instances there was a prompt change from the negative calcium balance to a state of equilibrium or to an even positive balance; usually, return of the serum calcium and phosphorus values to normal was also noted; in many instances, roentgenograms have shown evidences of recalcification of the skeleton, even to the point of disappearance of cysts and giant cell tumors. Deformities do not show early spontaneous correction of any proportion; spontaneous correction of deformities in adults must take a very long time (because of the slow reconstruction that goes on in the adult skeleton).

144. Geschickter, C.; Copeland, M. M., and Bloodgood, J. C.: Arch. Surg. **19**:169, 1929.

145. Alexander, E. G., and Crawford, W. H.: Ann. Surg. **86**:362, 1927.

146. Taylor, G. G., and Wiles, P.: Brit. J. Surg. **19**:606, 1932.

I have communicated with a number of those who reported cases of hyperparathyroidism in which parathyroidectomy was done. Hunter, who with Turnbull,¹⁴⁷ described four personally observed cases in comprehensive detail, wrote that the cases show further consistent progression of the healing since the report was published. Compere's¹⁴⁸ patient has done exceedingly well, as has Pemberton and Geddies's.¹⁴⁹ From others, I have likewise received communications confirming continued improvement.

The need for perseverance and persistence in the search for the offending parathyroid adenoma is well illustrated in the case reported by the Cornell and Harvard medical school groups. Several references were made in foregoing pages to this case,¹⁴⁹ and its remarkable course was recently summarized by Bauer.¹⁵⁰ Hitzrot and

147. Hunter, D., and Turnbull, A. M.: *Brit. J. Surg.* **19**:203, 1931.

148. Compere, E. L.: *Surg., Gynec. & Obst.* **50**:783, 1930.

149. Hannon, Shorr, McClellan and DuBois.²⁸ Bauer, Albright and Aub.¹¹⁸ McClellan and Hannon.¹²³

150. "This patient, a sea captain, was first recognized as a case of hyperparathyroidism by Dr. Eugene F. DuBois of New York in 1926. He has suffered from eight fractures. He has a marked kyphosis, considerable skeletal shortening and permanent bone deformities. His serum calcium has ranged between 13.1 and 16.5 mg. per 100 cc. The serum phosphorus varied from 1.4 to 3.2 mg. per 100 cc. The calcium and phosphorus excretions were markedly elevated. He was operated upon by Dr. E. P. Richardson in May, 1926, and in June, 1926. At each operation a parathyroid gland was removed, normal in appearance, but microscopic examination showed fatty infiltration. Removal of these two glands did not result in a cure, and the serum calcium and phosphorus, as well as the total calcium and phosphorus metabolism studies, remained unchanged. Despite a high calcium diet his symptoms and signs increased to such an extent that a third search was made for a parathyroid tumor in March, 1932, by Dr. Russel H. Patterson of New York City, but again no tumor was found. He was again transferred to the Massachusetts General Hospital in May, 1932. Examination at this time showed considerable increase in the severity of his disease. The decalcification had increased; there were many more bone cysts; questionable calcification of the kidney cortex (demonstrable on flat x-ray plate of the abdomen); kidney and ureteral stones; hypercalcemia and hypophosphataemia. Kidney function tests showed marked renal impairment evidenced by a non-protein nitrogen of 60 mg. per 100 cc. and a phenolsulphonphthalein excretion of 10 per cent in two hours' time. At three subsequent operations by Dr. Oliver Cope and Dr. E. D. Churchill, careful dissections of the various regions of the neck between the angles of the jaw and upper mediastinum were made; yet no parathyroid tumor or tissue was found. On November 2, 1932, an anterior mediastinotomy was done by Dr. E. D. Churchill. The parathyroid tumor, encased in a calcified capsule, was found; 90 per cent of it was excised, the remainder of the tumor was turned up on its pedicle and sewed in a superficial position in the region of the sternal notch. The serum calcium fell rapidly, and signs of tetany appeared on the third day. At this writing the serum calcium continues to fluctuate between 4.5 and 7.2 mg." (Bauer, W.: *J. Bone & Joint Surg.* **15**:135, 1933.) Since then the patient has died, and postmortem study confirmed the presence of the bone changes of hyperparathyroidism.

Comroe¹⁵¹ reported a case of osteoporosis, most likely caused by hyperparathyroidism, in which three normal parathyroid glands were removed. It seems to me that in all probability the condition will become progressively worse, as an undiscovered parathyroid adenoma surely exists.

The conclusive and dramatic effects so often obtained by the removal of adenomatous parathyroid tissue are not always sustained over an appreciable interval. The case reported by Boyd, Milgram and Stearns¹¹² is one in point. Dr. Boyd, in a recent personal communication (November, 1932), wrote:

Eighteen months after operation, this patient offered clinical, chemical and roentgenological evidence of relief from his condition. Bilateral osteotomies had been performed, and perfect healing had resulted. The density of the bones had returned to normal limits, so far as roentgenograms indicated. About six months ago, he returned to the hospital at our request, to serve as his own control for the completion of his metabolic study. It was discovered that his serum calcium against approximated 16 mg., his inorganic phosphorus 2.5 mg., per 100 cc. Other chemical data indicated a recurrence, yet there is no evidence of bone disease at present. Some general symptoms of hypercalcemia are becoming evident. He is now in the hospital under observation, and we hope soon to present for publication these findings that I have described to you, together with detailed metabolic data.

It may well be that in this case an additional parathyroid tumor exists. Hellstroem¹⁵² described a case in which there was temporary relief following the extirpation of an adenoma the size of a walnut; recurrent symptoms were entirely relieved by the removal of another parathyroid adenoma of about the same size. The case reported by Quick and Hunsberger¹¹¹ definitely showed that improvement is not to be expected if any of the adenomatous tissue is left behind (as in their case, owing to rupture of the enlarged gland during a difficult removal).

Postoperative Complications.—Removal of one or more parathyroid adenomas in the surgical treatment of these conditions has frequently been followed by parathyroid tetany. Often, on the day following operation, numbness and tingling in the fingers and toes occur; this may become worse; Chvostek's sign may appear together with other evidences of parathyroid tetany (prompt drop of the serum calcium). (The danger of tetany may possibly be reduced by a two-stage operation in which the adenoma or a part of it is first transplanted into the abdominal wall and removed several weeks later.) Precautions should therefore be taken immediately after operation to prevent the onset of tetany. Large amounts of calcium by mouth in the form of calcium lactate or other soluble calcium preparations are often effective. Owing to the rapid elimination of calcium, frequent administration is a desirable feature

151. Hitzrot, L. H., and Comroe, B. I.: Arch. Int. Med. **50**:317, 1932.

152. Hellstroem, J.: Acta chir. Scandinav. **69**:237, 1932.

of the calcium treatment (about every two or three hours). The dose should be large, as much as several grams of calcium daily (1 Gm. of calcium lactate is equivalent to approximately 130 mg. of calcium). When prompt effects are required, intravenous injection of from 5 to 10 cc. of calcium chloride may be necessary (10 per cent solution, slowly administered, leakage into surrounding tissues being avoided).

Owing to the rapid elimination of ingested or injected calcium, tetany may nevertheless develop. Therefore an agent which acts more slowly and the effect of which continues longer than the effect of ingested or injected calcium would be desirable in conjunction with the use of calcium. Parathyroid extract-Collip satisfies that requirement, and it has been used successfully when administration of calcium alone failed to prevent or to correct the tetany. Ten or 20 units of parathyroid extract may be given three or four times daily (subject to control by the determination of serum calcium). In addition, large therapeutic doses of viosterol may also be used. Such treatment may be continued for a number of weeks until the serum calcium values are definitely above the tetanic level. A low normal value of serum calcium may be stated as 9 mg. per hundred cubic centimeters. At a serum calcium value sufficiently close to that, there would be no danger of tetany due to hypocalcemia. Immediately after the operation, before adjustment has been accomplished, symptoms of tetany have been observed despite the fact that the serum calcium and phosphorus values were not sufficiently different from the normal to account for the tetany. Later, in one such case, the serum calcium fell to very low levels, and the injection of parathyroid extract-Collip and the administration of calcium by mouth proved ineffective until calcium was given intravenously (Barr and Bulger ²⁹). It is evident that the early management after the operation must vary with each case.

The reason for the development of the hypocalcemia and parathyroid tetany is not easily apparent; there has been much speculation on the mechanism of their appearance in clinical cases. Bodansky and I ^{31c} observed hypocalcemia in guinea-pigs several days after the discontinuance of prolonged treatment with parathyroid extract-Collip. We believed that this was most probably due to rapid redeposition of calcium in previously depleted tissues, associated with changes in the phosphorus balance. We also suggested that in experimental animals a temporary hypofunction of the normal parathyroid glands may have been caused by the prolonged treatment with parathyroid extract-Collip; immediately after the termination of the state of experimental hyperparathyroidism, hypofunction of the normal parathyroid glands contributed to the production of the complex of hypocalcemia, hyperphospho-

phatemia and a positive calcium and phosphorus balance, a complex which is often observed during the period of recovery in clinical cases. The same explanations were suggested for the analogous developments following the removal of parathyroid adenoma in Recklinghausen's disease.

Another common and disconcerting complication is oliguria, which may develop immediately after operation. Its cause is not known; When it occurs it corrects itself after a few days.

Attempts at Nonsurgical Treatment.—After the successful operative treatment had been established on a sound footing, and when the metabolic disturbances in hyperparathyroidism were better understood, some attempts were made to control the disease by nonsurgical measures. These attempts logically followed the advances in the understanding of the metabolic features in this disease; the reasons for undertaking such measures could well be understood in view of the existing general knowledge of mineral metabolism; however, certain of these nonsurgical measures (phosphate treatment) are not to be employed, as they may even aggravate the condition of patients with hyperparathyroidism. Therefore, when hyperparathyroidism is established in a patient, operative search for a parathyroid tumor should be undertaken as soon as the patient's condition warrants. I do not believe that it is a good policy to attempt to destroy such a tumor by irradiation.

The form of nonsurgical intervention on which most hope had been based was treatment with phosphates. Experience in administering phosphates in the form of sodium acid phosphate led Bulger, Dixon and Barr¹²² to suspect, from a theoretical point of view, important therapeutic possibilities. It seemed probable to them that if sufficient phosphate could be absorbed, serum phosphate might be increased and serum calcium lowered; if this alteration could be accomplished, they thought that the calcium metabolism might be restored to normal. Albright, Bauer, Claflin and Cockrill¹⁵³ also investigated the effects of ingestion of phosphate in clinical hyperparathyroidism (using monosodium phosphate and forcing fluids). They reported that the net result of such treatment is a tendency toward a positive balance of calcium phosphate and the alteration of the serum calcium and phosphorus values in the direction of normal. While a correction of the calcium-phosphorus metabolism may be attained by such measures, the effects are only temporary and, as pointed out,¹⁵³ not without danger. (The danger would be especially great if the serum phosphorus were elevated above normal; this would probably hasten death by increasing the supersaturation of the blood with phosphorus. Another danger of the ingestion of phos-

153. Albright, F.; Bauer, W.; Claflin, D., and Cockrill, J. R.: J. Clin. Investigation **11**:411, 1932.

phate is that it may aggravate the tendency to the formation of renal stones by increasing the phosphaturia). The condition of a patient on whom phosphate therapy was tried by these workers¹⁵³ nevertheless became progressively worse over a period of years; the course was summarized by Bauer.¹⁵⁴

In unpublished experiments, Bodansky and I have used phosphates in an effort to relieve dogs of the toxic effects of acute hyperparathyroidism. Sometimes, the results were startling: apathetic dogs, apparently moribund, would be relieved of the ill effects of overdosage of parathyroid extract within a few hours, and show a sharp drop in the serum calcium; at other times, the dogs died in spite of this treatment. At autopsy, congestion of the intestinal tract and metastatic calcification were observed; these changes are clearly established as being associated with fatal, acute hyperparathyroidism. The deleterious effects of phosphates in animals suffering from chronic hyperparathyroidism were recently further shown by the experiments of Grauer.¹⁵⁵ He stated that the intraperitoneal injection of sodium acid phosphate (from 0.25 to 1 cc. of a solution containing 0.075 Gm. per cubic centimeter) in guinea-pigs simultaneously receiving parathyroid extract-Collip exaggerated the decalcifying effects.

Viosterol has been used to promote recalcification of bone following removal of a parathyroid tumor. However, some have attempted to utilize it for nonoperative control of cases of Recklinghausen's disease; it seems to have no effect on the disease under such circumstances. In experimental hyperparathyroidism, Johnson¹⁵⁶ found that it did not prevent decalcification of the bones of either rats or dogs; if anything, the lesions were worse in the animals given viosterol. Likewise, Bodansky, Blair and I¹⁵⁷ noted that viosterol could not protect guinea-pigs from the demineralizing effects of parathyroid extract-Collip.

154. Bauer, W.: *J. Bone & Joint Surg.* **15**:135, 1933.

155. Grauer, R. C.: *Proc. Soc. Exper. Biol. & Med.* **30**:57, 1932.

156. Johnson, J. H.: *Am. J. M. Sc.* **183**:776, 1932.

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Notes and News

University News, Promotions, Resignations, Appointments, etc.—According to *Science*, Felix d'Herelle has resigned from the professorship of bacteriology which he has held at Yale University since 1927. While in residence Dr. d'Herelle confined himself largely to the study of bacteriophagy as a laboratory phenomenon, since suitable clinical material was lacking. It is the hope of elaborating his work in the clinical field, possibly at the new institute for infectious diseases at Tiflis, Russia, which now takes him abroad.

At Yale University H. M. Zimmerman has been promoted to a professorship of pathology.

In George Washington University E. B. Vedder has been appointed professor of experimental medicine and executive officer of the department of pathology and experimental medicine; J. L. Snyder has been appointed instructor in pathology, and Roger M. Choisser has been appointed professor of pathology.

Richard F. Thompson has been made assistant professor of bacteriology in Columbia University, New York.

The retirement on October 1 of Edwin O. Jordan as chairman of the department of hygiene and bacteriology in the University of Chicago has been announced. Dr. Jordan began his service in the University in 1892 and has been professor of bacteriology since 1907. He will be succeeded as chairman by William T. Taliaferro, professor of parasitology.

Edward L. Miloslavich, Milwaukee, has been appointed professor of legal medicine and director of the medicolegal institute at the Royal University of Zagreb, Yugoslavia.

Society News.—The second conference of the International Association for Geographic Pathology will be held in Utrecht during the last week of July, 1934, under the presidency of D. J. Josselin de Jong. The main topic of the conference will be arteriosclerosis; cirrhosis of the liver will be considered also. The association now has committees in twenty-eight countries. The executive committee consists of D. Josselin de Jong, Utrecht; Ludwig Aschoff, Freiburg-i-B.; Max Askanazy, Geneva; H. T. Karsner, Cleveland, and Gustaf Roussy, Paris. The chairman of the committee for the United States is Virgil H. Moon, Jefferson Medical College, Philadelphia. The annual dues are \$2.35 (10 Swiss francs). Each member receives a copy of the transactions. Membership is open to all who are interested.

The Third International Congress for Experimental Cytology will be held in Cambridge, England, August 21 to 26, 1933.

Carl V. Weller has been elected president, S. B. Wolbach president-elect, and C. P. Miller, Jr., secretary, of the American Society for Experimental Pathology.

At the twenty-sixth annual meeting of the American and Canadian Section of the International Association of Medical Museums, Victor C. Jacobsen was selected president, William Boyd vice-president and Maude A. Abbott secretary-treasurer.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

EFFECT OF ROENTGEN RAYS ON THE CENTRAL NERVOUS SYSTEM. R. S. LYMAN, P. S. KUPALOV and W. SCHOLZ, *Arch. Neurol. & Psychiat.* **29**:56, 1933.

Roentgen irradiation caused in four dogs both physiologic and structural changes. The former have been determined by observation of conditioned reflexes, which showed that diffuse cortical and subcortical changes had occurred. Histologic changes were also present, in the form of necrosis of scattered regions of the brain—occipital lobe, basal ganglions and optic chiasm.

Scholz, who studied the brains anatomically, sees the origin of the changes in the damage that irradiation is supposed to cause in the blood vessels—hyalinization and obliterating sclerosis—but not in the irradiation itself or in the possible inflammatory phenomena.

G. B. HASSIN.

CHROMATOLYSIS OF EFFERENT NEURONS. FREDERICK D. GEIST, *Arch. Neurol. & Psychiat.* **29**:88, 1933.

Geist studied in paraffin and celloidin sections the ganglion cell changes in various spinal and cranial nerves of monkeys and rabbits. The changes—chromatolysis or breaking up of the chromophilic granules—varied. The granules may undergo rearrangement; the cell itself may shrink, enlarge or fail to undergo any changes, and the nucleus may not change its location. The main factors instrumental in the ganglion cell changes are the type and age of the animal used and the distance from the central nervous system at which the nerve is injured.

G. B. HASSIN.

SUBARCUATE FOSSA OF TEMPORAL BONE OF MAMMALS: MORPHOLOGIC AND EMBRYOLOGIC RESEARCHES. L. CIURLO, *Arch. ital. di otol.* **43**:707, 1932.

Ciurlo made a study of the subarcuate fossa in the cranium of the human adult and fetus and many mammals. He describes its variations and its relations to the meninges, the cerebellum and the choroidal plexus of the fourth ventricle. He gives the details of the fossa in the embryos of cats, dogs, bats, etc., at different periods of their development. In the embryos of these mammals the subarcuate fossa is filled with mucous tissue and many small veins. It is only after birth that it is occupied by a lobule of the cerebellum. The veins of the fossa represent a branch of the posterior cerebral vein connected with the internal jugular vein. At an indeterminate time this branch is anastomosed with the superior petrosal sinus and forms its most internal portion.

NASAL FACTOR IN GENESIS OF ANAPHYLACTIC BRONCHIAL ASTHMA: CLINICAL OBSERVATIONS AND TREATMENT. E. RUBALTELLI, *Arch. ital. di otol.* **43**:738 (Dec.) 1932.

Rubaltelli studied a large number of patients with anaphylactic bronchial asthma, and found in a large percentage of them, besides nasal stenosis, a peculiar change in the form and structure of the ethmoid. Considering the nose as an organ of respiration and a reflex center, the author discusses the possibility of the direct and indirect mechanisms through which the nose may occupy first place in the etiology and pathogenesis of anaphylactic bronchial asthma. He concludes that in reality the nose holds an important place in the origin of this allergic disease,

either by the changed permeability of its mucosa or by its power of originating reflexes. From the therapeutic point of view, he asserts that prudent and partial operations on special portions of the nasal mucosa ameliorate the course of anaphylactic bronchial asthma because they reduce the zone of possible origin of the reflexes and modify the altered permeability of the mucosa itself.

HYPERTENSION AND MALIGNANT NEPHROSCLEROSIS IN NEGROES. R. H. JAFFÉ. *Centralbl. f. allg. Path. u. path. Anat.* **55**:209, 1932.

This report concerns the frequent occurrence of nephrosclerosis in Negroes, over 20 years of age, and serves to indicate the racial and sex incidence of this disease in 2,144 necropsies.

TABLE 1.—*Incidence of Malignant Nephrosclerosis*

	No. Autopsies	Malignant Nephrosclerosis	
		No. Cases	Per Cent
White men	972	9	0.92
White women	367	5	1.3
Negro men	476	24	5.0
Negro women	329	26	7.9

TABLE 2.—*Age Incidence*

	Under 60 Years, Per Cent	Average Age, Years
White men	88	50
White women	100	39
Negro men	96	42
Negro women	89	42

TABLE 3.—*Incidence of Hypertension*

	Number with Hypertension	Per Cent of Autopsies	Per Cent of Cases of Malignant Nephrosclerosis
White men	260	26.7	3.4
White women	86	23.4	5.6
Negro men	175	36.7	13.7
Negro women	102	31.0	25.4

The theory that Jaffé advances to explain the frequency of malignant nephrosclerosis is based on the change of climate experienced by Negroes who came from southern states to Chicago. Most of the Negroes dying of nephrosclerosis had been in Chicago only a short time.

GEORGE RUKSTINAT.

THE SECRETING TYPE, A MENDELIAN CHARACTERISTIC DEMONSTRABLE BY SEROLOGIC METHODS. F. SCHIFF and H. SASAKI, *Klin. Wchnschr.* **11**:1426, 1932.

Persons possessing agglutinogens A and B may secrete them in a concentrated form in the saliva, as may be shown by inhibition tests. The agglutinable factor of group O blood may also be demonstrated in saliva. Not all persons secrete antigens A, B and O in the saliva, since in almost one third of those examined, the inhibition tests were negative. The ability to secrete the antigens in the saliva is inherited as a simple mendelian dominant, as shown by studies of

50 families with 149 children, with the gene for the secreting type dominant over the gene for the nonsecreting type. The possible application of this new mendelian trait in medicolegal cases involving the question of paternity is discussed.

ALEXANDER S. WIENER.

THE SPECIFIC CHEMICOREACTIVE POSSIBILITIES OF TISSUE. BRUNO KISCH, München. med. Wchnschr. **79**:1947, 1932.

Simple chemical compounds specifically affect the respiration and the metabolism of different tissues of the body. The effects of fiftieth-molar and hundredth-molar solutions of alanine, serine, methylglyoxal, lactic acid and pyroracemic acid at 37 C. and in nutrient phosphate-free solution of p_H 7.4 on the respiration of the kidney, liver, diaphragm muscle, heart ventricle, retina and Jensen sarcoma tissues of the rat, guinea-pig, rabbit, cat, dog, cow, ox and pig are summarized in tabulated form. Respiration of the kidney is increased by alanine, that of the heart by pyroracemic acid and that of the retina by pyroracemic and lactic acids. Substances that increase the respiration of normal tissues have little effect on the respiration of tumor tissue.

The influences of these simple compounds should be studied from the pathologic and pharamacologic point of view, since they may be as important as the hormonal regulation of the tissue functions.

D. O. ROSBASH.

SYSTEMIC MESENCHYMATOUS EXHAUSTION: A NEW CONCEPTION OF OSTEOGENESIS IMPERFECTA. ERNST JECKELN, Virchows Arch. f. path. Anat. **280**:351, 1931.

In a new-born infant with osteogenesis imperfecta, the connective tissue in general was unchanged, there were areas of normal laminated bone and the resting cartilage was normal. In the regions of enchondral ossification and in the developing teeth, however, there were characteristic changes. These point to a primary inferiority of the mesenchyma, with beginning normal development, followed by an exhaustion of the bone-building mesenchyma leading to imperfect osteogenesis. This opinion differs from that of Bauer, who concluded that in this condition there is a primary congenital dysfunction or anomaly of the mesenchyma.

PERRY J. MELNICK.

INFLUENCE OF OBSTRUCTIVE JAUNDICE ON GASTRIC MOTILITY AND SECRETION. A. W. SELESNJEV, Virchows Arch. f. path. Anat. **280**:405, 1931.

An esophageal fistula and a gastrostomy were produced in four dogs; in three of these the common bile duct was ligated. Feeding experiments resulted in the following data: In the jaundiced dogs motility in general was not altered, although there was some retention after forty-eight hours. There was a gastric juice of very high acidity with much mucus. Individual differences, the mode of administration (whether by mouth or directly into the stomach) and the type of food produced some variations in the results. Ligation of the common duct produced marked widening of the bile ducts and a biliary cirrhosis of the liver.

PERRY J. MELNICK.

RELATIONSHIPS BETWEEN THE PANCREAS AND THE SEX GLANDS. R. BELKIN, I. MICHALOWSKY and L. FALIN, Virchows Arch. f. path. Anat. **280**:414, 1931.

In four cocks from which the pancreas and duodenum had been extirpated, the testes underwent severe atrophy and degenerative changes. These changes are not related to the general loss of weight which occurred, being out of proportion to it (normal, from 1:98 to 1:60; following pancreatectomy, from 1:232 to 1:298). They are not related to the hyperglycemia, because in animals made

hyperglycemic no testicular atrophy occurred. Injections of insulin in normal birds also produced severe loss of weight and testicular degeneration. A hormonal relationship is believed to exist between the pancreas and the sex glands.

PERRY J. MELNICK.

ORIGIN OF INFLAMMATORY TISSUE IN ACTINIA. E. MALOWITSCHKO, *Virchows Arch. f. path. Anat.* **280**:476, 1931.

To study inflammation in animals without a vascular system, *Actinia*, a species of Coelenterate, was selected. There are normally an ectoderm, an entoderm and a mesoglea derived from both in which are eosinophils, ameboid cells and fibrocytes. Silk threads were sewed into these animals, and microscopic studies were made on material fixed from a half-hour to seventy days later. The reactions were very similar to those in higher animals. At first, eosinophilic cells phagocytosed the destroyed tissue and disintegrated. Later ameboid cells attacked the silk fibers, even forming syncytial masses around them. Finally after seventy days the foreign material was surrounded by a capsule of collagen fibers.

PERRY J. MELNICK.

SITE OF DEPOSITION OF COAL DUST IN NORMAL AND PATHOLOGIC LYMPH NODES, WITH EXPERIMENTAL STUDIES OF THE RESORPTIVE POWERS OF LYMPH NODES. J. WÄTJEN and W. EILERS, *Virchows Arch. f. path. Anat.* **280**:487, 1931.

The site of storage of coal dust was studied in autopsy material. Also normal and infected chickens were given injections of india ink, and the carbon storage in the lymph nodes was studied. The site and amount of storage was found to depend on several factors: the amount of carbon, the length of time after the injection, the location of the lymph node, whether peripheral or central to the point of entrance, the state of activation of the reticulo-endothelium and the previous sclerosis of the reticulum. In general, in both peripheral and central nodes the endothelium of the sinuses was found to be the first site of deposition. The storage was greater and of longer duration if the lymph node was activated by an infection. The carbon is then transferred to the reticulum. After sufficient time all of it is in the reticulum unless previous fibrosis makes this impossible. These results differ from Nordmann's conclusion that in peripheral lymph nodes the reticulum is the primary site of deposition.

PERRY J. MELNICK.

EXPERIMENTAL HEMATOGENOUS TONSILLITIS. C. KRAUSPE, *Virchows Arch. f. path. Anat.* **285**:400, 1932.

By the injection of staphylococci and streptococci into the carotid artery of rabbits and cats, an acute, diffuse inflammation of the tonsils was set up. This reaction was often as superficial as that of the spontaneous necrotizing tonsillitis of rabbits, which is due to infection from the surface of the tonsil. When rabbits were sensitized by repeated injections of streptococci subcutaneously, injection of the same strain into the carotid artery caused lesions that were more circumscribed than those caused by the same organism in nonsensitized animals. Such lesions consisted chiefly of histiocytes. Similar small granulomatous lesions were seen also in the tongue, myocardium and kidney. The injection into the carotid artery of bacteria-free, toxin-containing filtrates of streptococci caused inflammatory changes in the tonsils.

O. T. SCHULTZ.

INCIDENCE OF DISEASE IN JAVA. A. E. SITSEN, *Virchows Arch. f. path. Anat.* **285**:506, 1932.

This contribution to geographic pathology, which cannot always be sharply delimited from racial pathologic or pathologic anthropology, is based on 3,198 necropsies, of which 173 were done at Batavia and 3,025 at Surabaya, during the

years 1909 to 1927. These data are compared with those derived from the necropsies at Innsbruck in the years 1926 to 1930. In the Java series most of those who came to necropsy were Malays. Exact comparison between the two series of data, even excluding the racial factor, is not possible because of differences in the age groups represented in the two series of necropsies and because of incomplete vital statistics in Java. To mitigate these factors as much as possible the mathematical principles involved are discussed, and a formula is worked out for comparing the actual incidence in the Java series with the expected incidence on the basis of the Innsbruck data. In the Java series the actual percentages of some of the more important diseases were: pneumonia, 33; tuberculosis, 23, and intestinal amebiasis, 8 per cent; circulatory diseases, renal disease and hepatic cirrhosis ranked fifth in point of frequency, with 4 per cent each. Malignant tumors and syphilis each made up 2.5 per cent of the total. The figures for the diseases more characteristic of tropical or subtropical regions, exclusive of intestinal amebiasis were: beri-beri and malaria, each 2 per cent; ankylostomiasis and tropical abscess of the liver, each 1 per cent.

O. T. SCHULTZ.

FUNCTION OF THE RENAL TUBULES. G. EKEHORN, *Virchows Arch. f. path. Anat.* **285**:605, 1932.

In previous articles of a series devoted to renal physiology, various problems have been discussed, analyzed and summarized. In the last preceding article the conclusion was reached that the glomerular liquid is an ultrafiltrate, which is much more dilute than urine and is formed in much larger quantity. In this contribution, apparently the last of the series, the function of the renal tubules is discussed. All the articles of the series have been based on the author's "On the Principles of Renal Function," published in 1931 as supplement 36 to *Acta medica Scandinavica*. The author concludes that in the kidney with normally functioning glomeruli the tubules secrete or excrete none of the urinary constituents that are preformed in the plasma. The function of the tubules is resorption of the glomerular filtrate. Only creatinine and perhaps sulphates are not resorbed. The resorbed material contains not only water and preformed plasma substances that appear in the final urine, but diffusible substances that do not appear in the bladder urine. The resorbed material varies in quantity and composition under varying conditions. Resorption by the renal tubules is a vital process that is regulated by hormones, ions and perhaps excretable substances of the plasma.

O. T. SCHULTZ.

RESISTANCE OF MEGAKARYOCYTES TO EXPERIMENTAL CONDITIONS. P. W. SSIPOWSKY, *Virchows Arch. f. path. Anat.* **285**:723, 1932.

Fully grown rabbits were subjected to a variety of procedures to determine the resistance of the megakaryocytes of the bone marrow of the femur to the procedures used. The latter were ligation of the veins to produce stasis, ligation of the artery to cause local anemia, application of heat and cold, production of an acute infection and the use of hemolytic substances. To all these procedures the megakaryocytes were less resistant than the other elements of the marrow. The changes were degenerative: pyknosis, karyorrhexis and plasmorrhexis. Marked pyknosis of the megakaryocytes was evident before any changes could be seen in any of the other cells. Reestablishment of the circulation after ligation of the vein was followed by a return of the megakaryocytes to normal.

O. T. SCHULTZ.

EFFECT OF SECTION OF BOTH VAGI ON THE STOMACH. J. M. LASOWSKY and A. N. PTSHELINA, *Virchows Arch. f. path. Anat.* **285**:755, 1932.

In the dog, section of both vagi above the diaphragm was not followed by the formation of erosions or ulcers of the stomach. Secretion of mucus by the mucous

cells was increased, and some of the chief cells contained mucus. The secretory granules disappeared. These alterations are similar to those of chronic gastritis, and are therefore not characteristic of the latter condition. O. T. SCHULTZ.

GENERALIZED TROPHIC DISTURBANCES FOLLOWING EXPERIMENTAL INJURY TO THE DENTAL NERVES. P. N. KARTASCHOW and L. M. MATWEEWA, *Virchows Arch. f. path. Anat.* **286**:11, 1932.

In dogs, the pulp cavity of one or two teeth was exposed. A small quantity of croton oil or arsenic paste was introduced into the pulp, after which the opening into the tooth was sealed with cement. The animals appeared well after the dental operation. But two or more months later their appetite failed, they lost weight, the hair fell out and the animals died as the result of acute gastro-enteritis. These disturbances developed more quickly in young dogs than in older ones, and in both young and older animals the advent of serious symptoms was hastened by repeated spinal tappings. The authors interpret the symptoms as trophic disturbances. Chemical trauma to the dental nerves leads to reactive changes in the central nervous system. The latter may be of such a character and grade that the symptoms resemble those of encephalitis. Recovery from an encephalitic attack may be followed by recurrence. Disturbances of nervous regulation, due to central nervous system changes, lead to alterations of the physicochemical balance of the organs.

O. T. SCHULTZ.

EXPERIMENTAL SCLERODERMA DUE TO PARATHYROID HORMONE. H. SELYE, *Virchows Arch. f. path. Anat.* **286**:91, 1932.

The author gives a concise review of the history, clinical manifestations, pathology and theories of scleroderma in human beings. In his own experimental work, which was done in the school of hygiene of the Johns Hopkins University, nursing rats from 7 to 14 days old received a daily intraperitoneal injection of from 5 to 10 units of parathyroid extract-Collip for three or four successive days. In 20 per cent of the animals changes occurred that the author considers identical with those of scleroderma in human beings. These changes began after the second dose of the parathyroid extract, the early changes being similar to those of the edematous stage of scleroderma. Then followed an indurative stage, and the atrophic stage was reached in about fifteen days. Animals that received only a single course of three or four daily injections recovered, and two months after the first administration the skin had returned to normal. The author thinks that hyperparathyrosis is not a disease entity, but that there are several forms of hyperparathyrosis characterized by different clinical and pathologic states. An excess of parathyroid hormone brings about a condition of the body that manifests itself in a variety of disease pictures. Among these he includes scleroderma, osteitis fibrosa cystica and Albers-Schoenberg marble disease of bone. In a number of other syndromes, Paget's disease of the bone, von Recklinghausen's neurofibromatosis, progressive hemiatrophy of the face and periarteritis nodosa, in which parathyroid hyperactivity has been postulated, the relationship of hormone and disease is not so clear. The article, which is not unduly long, contains 191 references to the literature.

O. T. SCHULTZ.

FUNCTIONS OF THE RETICULO-ENDOTHELIAL SYSTEM. R. FREUND, *Virchows Arch. f. path. Anat.* **286**:526, 1932.

With a gold sol, Freund found it possible to obtain much more uniform vital storage by the reticulo-endothelial cells than with substances previously used. Treatment of the animals with an electrocolloidal copper solution inhibits the vital storage of gold for forty-eight hours. Vital storage of gold after copper treatment was used by the author as an indicator in a variety of experiments planned to study the functional activities of the active mesenchyme. It was not possible to

influence antibody (hemolysin) formation, anaphylaxis or the chemotherapeutic response in experimental mouse trypanosomiasis. A variety of pharmacologic substances, such as the hormones, calcium, potassium, histamine and caffeine, yielded different vital storage pictures, depending on the effect of the substance used on the circulation of the organ. The reticulo-endothelial system has a variety of functions which may be influenced separately and each of which may therefore be looked on as a partial function of the cell. In the regulation of these functions, the blood stream is the underlying factor. It influences function by its composition, by the physicochemical properties of its contained substances and most of all by its rate of flow through the organs.

O. T. SCHULTZ.

DEPOSITION OF CHOLESTEROL IN THE LUNGS AFTER INTRAVENOUS INJECTION.

G. A. MERKULOW, *Virchows Arch. f. path. Anat.* **286**:571, 1932.

A finely dispersed colloidal preparation of cholesterol in dextrose or levulose solution was injected intravenously into animals, chiefly rabbits. The cholesterol content of the preparation varied from 3 to 20 per cent and the quantity of solution injected from 5 to 32 cc. Single or repeated injections were made, and the animals were killed at intervals of from twenty minutes to twenty-five days after injection. The deposition of cholesterol in finely particulate form in the capillaries of the lung began almost immediately after injection and continued for several days, the particles becoming larger. Esterification of the cholesterol began on the fifth day after injection. After repeated injections the cholesterol deposit assumed a crystalline form. After the longer intervals and after repeated injections, intimal proliferation occurred in the vessels in which cholesterol had been deposited. The injection and the early deposition were followed by the accumulation of leukocytes in the capillaries of the lung and by transient peripheral leukocytosis. The latter was followed by leukocytic infiltration along the arteries of the lung. The levulose cholesterol sol often caused diffuse thrombosis of the small vessels of the lung.

O. T. SCHULTZ.

Pathologic Anatomy

CALCIFIED PULMONARY MILIARY TUBERCULOSIS. BARNET P. STIVELMAN, *Am. Rev. Tuberc.* **26**:437, 1932.

Chronic miliary tuberculosis of the lungs is of rare occurrence being observed 4 times in over 8,500 tuberculous patients who were subjected to thorough physical and roentgenographic examinations. Among the early reports is that of Wunderlich in 1860. Longcope described 6 cases in 1906, and Northrup in 1914 was probably the first to show roentgenologic evidence of chronic miliary tuberculosis of the lungs in a boy of 6 years. Since then reports have increased. The disease is of more than academic interest, and is not necessarily of the gravest prognostic import when involving a part of or an entire lobe of the lung. On the other hand, miliary involvement of both lung fields almost invariably evokes a fatal prognosis. The author presents a bilateral case with roentgenogram in a Negress, 31 years of age, and discusses the differential diagnosis from broncholithiasis and miliary carcinomatosis.

H. J. CORPER.

MASSIVE ATELECTASIS COMPLICATING PULMONARY TUBERCULOSIS. LOUIS I. SOKOL, *Am. Rev. Tuberc.* **26**:442, 1932.

A boiling down of the various definitions presented in the literature yields the following conception, which may be considered applicable to all types of massive atelectasis; an acute or subacute febrile complication, produced by the obstruction of a bronchus and followed by a more or less complete absorption of vesicular air in the corresponding portion of the lungs, thus giving to the organ a structure resembling the fetal lung. It is characterized by the clinical symptoms of unilateral

pulmonary consolidation, with displacement of the mediastinum and its contents toward the affected side. Massive atelectasis was known as long ago as 1844, when it was first reported by Legendre and Bailey. Etiologic causes may be (1) intrabronchial, (2) extrabronchial and (3) idiopathic. Two cases are reported by the author: (1) one of extrabronchial origin, caused by a fibrous strand, and (2) the other intrabronchial, caused by plugging by a blood-clot or cast. Atelectasis must be differentiated from pneumonia, spontaneous collapse and pleurisy with effusion, as well as from acute dilatation of the heart, infarction, diaphragmatic hernia, pulmonary embolus and thrombosis.

H. J. CORPER.

PATHOLOGIC PECULIARITIES OF TUBERCULOSIS IN THE AMERICAN NEGRO.
MAX PINNER and JOSEPH A. CASPER, *Am. Rev. Tuberc.* **26**:463, 1932.

The postmortem findings in 303 Negroes and 219 white patients who died of tuberculosis are compared. The differences noted were a greater frequency of miliary tuberculosis in the Negro (37.3 per cent as compared with 15.5 per cent of the white patients), a greater frequency of hematogenous metastases in the Negro (84.2 per cent to 40 per cent), a greater frequency of lymphatic metastases in the Negro (66.8 per cent to 10.8 per cent) and various qualitative differences in the pattern of the tuberculous lesions. Infection tends to produce a high state of allergy in the Negro, but he does not readily acquire a state of increased resistance coincidentally. Lack of infection in childhood does not exist in the Negro. The authors believe a true genotypic difference exists between the Negro and white races, accounting for their different reaction to tuberculosis.

H. J. CORPER.

PATHOGENESIS OF THE CHANGES IN THE CEREBROSPINAL FLUID IN MENINGITIS.
FRANK FREMONT-SMITH, *Arch. Neurol. & Psychiat.* **28**:778, 1932.

The author defines meningitis as an infection of the cerebrospinal fluid which largely originates "in the arterial blood in the capillaries of the choroid plexuses" and probably also comes from "other sources." Fremont-Smith likens the cerebrospinal fluid in meningitis to an abscess. In meningitis the pressure of the cerebrospinal fluid is increased, as are the cell and protein contents. The contents of sugar and chlorides are in contrast decreased, but a quantitative relationship between the increase in protein and the decrease in chlorides is most likely due to the decrease of chlorides in the plasma of the blood. On the whole, the chemical composition of the cerebrospinal fluid in meningitis depends chiefly on the composition of the blood plasma.

G. B. HASSIN.

HISTOLOGIC STUDIES IN MENINGITIS. GEORGE B. HASSIN, *Arch. Neurol. & Psychiat.* **28**:789, 1932.

The four commonest types of meningitis (purulent, cerebrospinal, tuberculous and pneumococcic) are described in detail with reference to the cell changes in the subarachnoid space and the condition of the perineurial and endoneurial prolongations of the meningeal spaces and cerebral parenchyma. Perineuritis is always present more or less, and affects the subarachnoid spaces and the parenchyma of the brain as well, causing rarefaction, hydrocephalus and edema. The mesothelial cells exhibit, with other meningeal cells normally present in the subarachnoid space, a marked meningitic reaction but no phagocytic activities. They exhibited a reaction in a case of an acute mental disorder. It was similar to that produced experimentally by a subarachnoid injection of laked blood, lampblack and similar products, and is generally designated aseptic meningitis. Such a type of meningitis in a mental disorder should be considered the result of the action of chemical substances discharged by the brain into the subarachnoid space.

AUTHOR'S ABSTRACT.

SO-CALLED NONSUPPURATIVE ENCEPHALITIS AND ENCEPHALOMYELITIS. JOSEPH H. GLOBUS, Arch. Neurol. & Psychiat. **28**:810, 1932.

Globus would restrict the term encephalitis to inflammatory conditions of the brain caused by an infectious agent. He gives a brief review of the histologic changes in various forms of encephalitis, and admits that it is not possible to differentiate them on "geographic and cytologic grounds." The cerebral changes produced by toxins or inorganic poison, such as lead, should not be classified, says Globus, as encephalitis, for morphologic manifestations of inflammatory disease process are absent.

G. B. HASSIN.

THE BRAIN IN ACUTE RHEUMATIC FEVER. N. W. WINKELMAN and JOHN L. ECKEL, Arch. Neurol. & Psychiat. **28**:844, 1932.

The brain is among the organs which are usually involved in rheumatic fever, permanent cerebral manifestations usually depending on an endocardial condition. As a rule, however, the changes in the brain are transient. The clinical picture may be dominated by choreic movements or may resemble that of lethargic encephalitis.

The authors studied five cases, and consider the changes to be similar to those present in any general infection; that is, they are not specific. In one of their cases the changes were probably due to cerebral emboli that resulted from loosening of the small particles of the cardiac valves. The brain changes were not due to hyperpyrexia and were present also in the parenchyma (cloudy swelling) and in the mesodermal tissues, of which the most significant were the so-called productive endarteritis of the small blood vessels and edema of the brain. Real inflammatory phenomena were lacking; in some cases so-called acellular cortical areas of destruction were in evidence.

G. B. HASSIN.

NERVE DEGENERATION IN POLIOMYELITIS. W. P. COVELL, Arch. Neurol. & Psychiat. **28**:1056, 1932.

The site of the functional loss in poliomyelitis, produced experimentally in monkeys, is in the ganglion cells of the anterior horns or at their synapses with the upper motor neuron. The duration of the paralysis in Covell's experiments was not more than forty-eight hours. The extent of the injury to the cells was studied in the lower cervical, dorsal and lower lumbar regions of the spinal cord. The greatest number of ganglion cells destroyed was in the intermediate, dorso-lateral and ventrolateral groups of the spinal cord, and more than half of the cells were destroyed in the first twenty-four hours of paralysis. After twelve hours of paralysis, the ganglion cells exhibited marked polymorphonuclear cell neuronophagia (63.6 per cent of the neuronophages were polymorphonuclear leukocytes), which progressively decreased, being only 24.3 per cent after thirty-six hours; the remaining cells were other phagocytes. The degree of damage to the ganglion cells as well as to the spinal roots and peripheral nerve fibers was also studied by means of intravenous injections of neutral red dye. It stains deeper the parts that are destroyed, the ventral horn cells and the ventral roots of the spinal cord. In early stages, it becomes clumped to one side of the nucleus of the damaged ganglion cell; in the later stages it shows in the cytoplasm as minute globules.

G. B. HASSIN.

ENCEPHALITIS DISSEMINATA. JAMES C. GILL and RICHARD RICHTER, Arch. Neurol. & Psychiat. **28**:1072, 1932.

In a man, aged 23, a right-sided hemiparesis suddenly developed with ipsilateral ptosis and facial paresis. About eleven months later a weakness appeared on the left side, while that of the right side disappeared, and a paralysis of the right

facial nerve developed. The patient was lethargic, and swallowed with difficulty. Serologic and other findings were negative; the blood picture was normal, but the temperature became elevated shortly before death, which occurred one month after the onset of the second attack.

Necropsy revealed numerous foci of softening in the white substance, especially in the right hemisphere; microscopically, foci of demyelination were present, which contained masses of fat granule bodies in many instances. Other changes were in the axons, with numerous astrocytes and a marked increase of neuroglia fibers at the edge of the focus. The cortex and basal ganglions were not involved. The blood vessels showed infiltration with gitter cells mixed with lymphocytes and plasma cells; no foci of softening were present in the basal ganglions, pons or cerebellum, but a lymphocytic infiltration was sometimes marked. In short, multiple degenerative softening was microscopically associated with inflammatory phenomena in the brain stem, which the authors consider not secondary to the massive degenerative phenomena, but independent. The authors evidently had great difficulty in classifying their case. It looked to them like disseminated encephalomyelitis, multiple sclerosis and Schilder's disease, which they would all include in the group of nonsuppurative infectious encephalomyelitis.

G. B. HASSIN.

THE NONSPECIFICITY OF THE HISTOLOGIC LESIONS OF DEMENTIA PARALYTICA.
FREDERIC WERTHAM, Arch. Neurol. & Psychiat. **28**:1117, 1932.

Chickens were inoculated with *Spirochaeta gallinarum* and their central nervous system studied by Wertham histologically. The sections, embedded in celloidin, measured 12 microns. The meninges, especially the cerebral, were in some cases slightly infiltrated with lymphocytes and plasma cells. Ganglion cell changes were more or less in evidence (shrinkage and pyknosis, so-called severe cellular disease and cellular vacuolation). The vessels showed hyperemia, and in the smaller blood vessels there was frequently an adventitial infiltration with plasma cells and large amounts of iron. The glia exhibited proliferation in the form of small clusters, which were frequent in the cerebellum, medulla and forebrain. There were numerous Hortega cells (called Hortega glia by Wertham) in the form of sausage cells, and they often contained iron. In nature and distribution, this corresponded to the iron found in dementia paralytica, for which it is generally considered specific and called dementia paralytica iron. In the spinal cord there were glia clusters in the dorsal columns and also small foci of demyelination (probably artefacts). However, the foregoing histologic features (plasma cell infiltration, proliferation of Hortega cells and the presence of dementia paralytica iron) were also found in a number of control chickens; that is, a picture closely resembling that of dementia paralytica in man and spirochetosis gallinarum may be a spontaneous disease in chickens, and need not cause any clinical symptoms.

G. B. HASSIN.

TORSION OF THE OMENTUM. J. H. MORRIS, Arch. Surg. **24**:40, 1932.

Morris reviews the literature and adds 3 personally observed cases, to bring the total reported to 217. Torsion of the omentum occurs on its long axis and may be acute, with complete infarction, or recur as a result of incomplete rotation. Preoperative diagnosis is rare, less than 8 per cent of the cases having been correctly diagnosed. A frequent initiating factor is the fixation of the free end of the omentum to an inflammatory focus or to an operative scar. The torsion therefore may be classified as unipolar when the lower end is free and bipolar when the lower end is fixed. The most frequent associated lesion is hernia. In cases not associated with hernia, cysts, tumors and regional inflammatory processes are to be considered as contributing etiologic factors. The changes are congestion, edema, thrombosis, hemorrhagic infarction and necrosis.

N. ENZER.

CONGENITAL CYSTIC DILATATION OF THE COMMON BILE DUCT. M. M. ZINNINGER and J. R. CASH, Arch. Surg. **24**:77, 1932.

The authors report at length a case of cystic dilatation of the common bile duct in which the cyst was about 10 cm. in diameter. It was lined by well preserved mucosa, similar in structure to gallbladder mucosa. The cystic duct emptied into the cyst, and the cyst in turn emptied into the duodenum by a duct joined just before its terminal end by the pancreatic duct. Eighty-two cases were discovered in the literature, and these are reviewed in detail. The theories presented indicate that this condition is generally recorded as a congenital anomaly, although there is some belief that it is idiopathic in formation.

N. ENZER.

TRAUMATIC NECROSIS OF THE LIVER WITH EXTENSIVE RETENTION OF CREATININE AND HIGH-GRADE NEPHROSIS. F. C. HELWIG and T. J. ORR, Arch. Surg. **24**:136, 1932.

In a young boy severe traumatic necrosis of the liver developed as the result of an automobile injury, and he died on the eleventh day of illness. The nonprotein nitrogen of the blood rose to 240 mg. per hundred cubic centimeters and the creatinine of the blood to 25 mg. Necropsy revealed intraperitoneal hemorrhage, a large, swollen, pulpy liver and greatly swollen, hyperemic kidneys. Microscopic examination revealed areas of necrosis and hemorrhage in the liver with some evidence of an acute inflammatory reaction and extensive parenchymatous degeneration of the cortex and tubules of the kidney. There was no evidence of fatty degeneration in the kidney. The authors were able to find only one other case in the literature, reported in 1927, by Furtwaengler. In this case bilateral necrosis of the renal cortices occurred. The authors believe that the renal damage was the result of a toxin, elaborated in the areas of hemorrhagic necrosis in the liver.

N. ENZER.

THE SPLENIC LESION IN HEMOLYTIC JAUNDICE. WILLIAM P. THOMPSON, Bull. Johns Hopkins Hosp. **51**:365, 1932.

Hemolytic jaundice is a clinical and pathologic entity which exhibits typical splenic changes. In a study of thirty such spleens enlargement was noted on gross examination (average weight, from 1,000 to 1,500 Gm.). On microscopic study the venous sinuses were enlarged and frequently empty. The sinus endothelium, bulging into the sinus lumen, was hypertrophied. The malpighian bodies were small and widely scattered. The pulp, which presented the most characteristic feature of the microscopic appearance, was a mass of closely packed red cells. There was no increase in the connective tissue or the iron pigment. In short, the splenic changes in this condition are so typical that the diagnosis of hemolytic jaundice is readily made on the finding of dilated venous sinuses, prominent sinus endothelium, small, scattered malpighian follicles and pulp densely packed with erythrocytes.

E. KLEIN.

SO-CALLED ATYPICAL LYMPHOGRANULOMATOSIS. C. STERNBERG, Beitr. z. path. Anat. u. z. allg. Path. **87**:257, 1931.

The author preliminarily reviews the characteristic histology of lymphogranulomatosis and emphasizes that in the absence of the characteristic giant cells the diagnosis is unjustified. There are instances in which the cells are so large and atypical as to occasion the suspicion of sarcoma. But even here there is definite polycellularity, a tendency to fibrosis and necrobiosis. The possibility of a transition to sarcoma in such cases is denied by the author. He further cautions that the diagnosis of lymphogranulomatosis is at present a histologic one and should never be confused with the term atypical.

W. S. BOIKAN.

THE PLASMA CELL REACTION OF THE SPLEEN, ESPECIALLY IN CARCINOMA.
I. MÜLLER, *Centralbl. f. allg. Path. u. path. Anat.* **55**:180, 1932.

This author investigated the plasma cell reaction of fifty-four spleens, twenty-five of which were obtained from bodies in which carcinoma occurred. The number of plasma cells in the spleen was unrelated to the number, size or situation of carcinomatous metastases in the body. The plasma cell reaction was most marked when the tumors were necrotic, so considerable quantities of protein came into the circulation before death. Some spleens had a very slight reaction where the tumor had been removed by operation. In spleens from persons who had died of caseous pulmonary tuberculosis there was a rich plasma cell reaction, whereas it was absent in the spleens of people who had died of trauma or chronic heart disease. The explanation of this reaction is found in the filtering activity of the spleen called forth by protein, from the aforementioned lesions, in the blood. In carcinoma, formed cellular elements call forth this reaction after disintegration. This reaction may explain the well known immunity of the spleen to tumor.

GEORGE RUKSTINAT.

CYSTIC DILATION OF THE PERITONEAL LYMPH VESSELS IN TUBERCULOSIS.
E. SIEDECKI, *Centralbl. f. allg. Path. u. path. Anat.* **55**:183, 1932.

In the body of a 22 year old woman who died of pulmonary laryngeal, bronchial and intestinal tuberculosis long-stalked cysts were found pendant from the small bowel serosa in the region of mucosal ulcers. The largest cyst, 13.7 cm. long, 1 cm. across at the base and 3 cm. at its bulbous end, was at the junction of the jejunum and ileum, and two others were respectively 30 and 50 cm. distal to it. Microscopically these cysts were dilated lymph channels the efferent patch of which had been obstructed by tubercle formation and inflammation in the region of an ulcer. Presumably the inflow of lymph was not impaired, and the cysts resulted. The name "lymphangiectasiae cysticae peritonaei" is suggested for such structures.

GEORGE RUKSTINAT.

A SUPRARENAL GLAND STONE. E. PETRI, *Centralbl. f. allg. Path. u. path. Anat.* **55**:292, 1932.

In the body of a 54 year old man, who had suffered from cardiac decompensation and who died of empyema of the pleura, the left suprarenal gland was about one third the usual size. Its medulla was occupied by a date pit-sized stone, yellowish-gray and somewhat crumbly. On analysis the stone was found to contain 4.7 per cent of calcium, principally calcium phosphate, 7 per cent cholesterol and traces of iron. The cortex of the gland was poor in lipid, compressed but still recognizable. In addition to the stone the medulla contained only thick collagenic connective tissue masses, in the inner layers of which were calcium rests and slits from dissolved cholesterol. Petri suggests that a primary closure of the medullary veins followed by total necrosis of the medulla may have preceded the stone formation. He cites the chronic cardiac ailment as a basis for the formation of marantic thrombi and the compatibility of such a unilateral lesion with life.

GEORGE RUKSTINAT.

PERITONITIS ORIGINATING IN INTESTINAL ENDOMETRIOSIS AS A COMPLICATION OF PREGNANCY. F. HAUFLE, *Virchows Arch. f. path. Anat.* **280**:822, 1931.

A woman, aged 30, had acute intestinal symptoms that led to a diagnosis of acute appendicitis in the sixth month of her first pregnancy. At operation generalized peritonitis was discovered. On the serous surface of a loop of small intestine were found a number of small abscesses, to which the peritonitis was ascribed. A portion of intestine 17 cm. long was resected. Gross examination of this revealed a number of small, firm, subserous nodules, as well as several small

abscesses. The mucosa appeared normal. On microscopic examination the nodules were found to be composed of endometrial tissue. The epithelium of the glands had undergone the changes of the endometrial glands during pregnancy, and the surrounding stroma had been transformed into decidua. At one point microscopic examination revealed a communication between a narrow cleft of the mucosa and a gland of an endometrial nodule. The lumen of this passage was filled with leukocytes. The involved intestine came from the jejunum. The author is convinced that a communication existed between the lumen of the intestine and the endometrioid glands, and that infection occurred when the endometrioid tissue underwent the changes of pregnancy.

O. T. SCHULTZ.

ARE LOCALIZED APICAL THICKENINGS OF THE PLEURA TUBERCULOUS IN ORIGIN? A. BESSIN, *Virchows Arch. f. path. Anat.* **280**:837, 1931.

Many observers look on the localized, cartilage-like areas of thickening of the pleura that are seen so frequently, especially in elderly persons, at or just below the apex of the lung, as the scars of a healed tuberculous infection. In order to determine whether such lesions are tuberculous in origin, Bessin examined a series of them histologically and injected the ground material into guinea-pigs. The material selected for study came from twenty-seven cases in which at necropsy there was no macroscopic evidence of tuberculosis. In none of the twenty-seven cases did the pleural scar reveal any histologic evidence of tuberculosis. In only two instances did tuberculosis develop in the inoculated animal. The author concludes that in the great majority of cases localized apical thickening of the pleura is due not to tuberculosis but to mechanical factors.

O. T. SCHULTZ.

CONGENITAL SYPHILIS OF THE INTESTINE. D. Y. KU, *Virchows Arch. f. path. Anat.* **280**:852, 1931.

Ku reports four cases of congenital syphilis with syphilitic involvement of the small intestine. He describes three histopathologic types of lesion. In one the mucosa was atrophic and was replaced by granulation tissue. Miliary syphilomas were present in the muscle coat. In a second case there was diffuse thickening of the wall owing to proliferation of the connective tissue of the mucosa and sub-mucosa. In a third form, necrotic gummatous lesions of the mucosa and sub-mucosa were associated with ulcers. Spirochetes were found in the tissues of the intestinal lesions in two of the cases.

O. T. SCHULTZ.

VARIATIONS IN THE SHAPE OF THE NUCLEUS PULPOSUS OF THE INTERVERTEBRAL DISKS. R. BÖHMIG, *Virchows Arch. f. path. Anat.* **280**:873, 1931.

In a previously published study of the vertebral column from its early embryonic development to the completion of development of the vertebral bodies during the early part of the third decade of life, the author described variations in the form of the nucleus pulposus that he held to be developmental in origin. Such bottle-shaped and double V-shaped nuclei he believed to be the result of the growth of the tissue of the nucleus into the canal of the primitive notochord. Schmorl considered such variant forms of the nucleus pulposus and the down-growth of cartilaginous nodules from the disk into the spongy bone of the body, when they occur in older persons, to be pathologic in origin and to be due to microfractures of bony trabeculae and other mechanical damages. Böhmig now describes nucleus identical with those seen in the earlier periods of life. Contrary to Schmorl's belief, he holds that these also are developmental in origin. Segmentation of the nucleus into two or more round or oval masses separated by fibrous tissue or fibrocartilage also occurs both before and after the age of 30 and is developmental in nature and not pathologic.

O. T. SCHULTZ.

TWO CASES OF PRIAPISM. S. SCHEIDEGGER, *Virchows Arch. f. path. Anat.* **283**: 178, 1932.

The condition in each case began a few days before death and persisted after death. The onset was preceded in each case by an infection of the upper part of the respiratory tract. In the first patient, aged 62, there were found at necropsy an early polypoid carcinoma of the rectum and thrombosis of the pelvic venous plexus. The blood sinuses of the corpora cavernosa were distended by recently thrombosed blood, in which no tumor cells were found. The sinuses of the corpus spongiosum were empty. The second patient, aged 28, had taken a yohimbine preparation at irregular intervals, the last time a few days before the onset of priapism; this was ushered in with subcutaneous hemorrhages of the thighs, scrotum and penis. Necropsy revealed widespread, partly purulent thrombosis of the pelvic veins and distention of the sinuses of the corpus spongiosum by blood that was still liquid after death. The corpora cavernosa were empty. The walls of the smaller pelvic vessels were necrotic. The second case is interpreted as a septic thrombosis of the pelvic veins occurring in the course of a generalized infection, the localization of the process in the pelvic vessels being the result of dilatation of the vessels brought about by the action of yohimbine.

O. T. SCHULTZ.

INTRAVASCULAR PRESSURE AS THE CAUSE OF ARTERIOSCLEROSIS. E. MOSCOWITZ, *Virchows Arch. f. path. Anat.* **283**:282, 1932.

Fifty necropsies that revealed arteriosclerosis of the pulmonary artery and its branches are analyzed and the findings discussed in relation to the author's thesis that intravascular pressure, normal or increased, is the essential factor in the pathogenesis of arteriosclerosis. The necropsies were done at the Mount Sinai Hospital, New York, during the years 1926 and 1927, and formed part of a total of 770 necropsies at that hospital during these two years. This material formed the basis of articles previously published (*Am. J. M. Sc.* **174**:388, 1927; **178**:244, 1929) in which, as in the present communication, the author presents the deductions that uphold his thesis.

O. T. SCHULTZ.

CONGENITAL MALDEVELOPMENT OF THE LARYNX. ANNEISE ROHRMANN, *Virchows Arch. f. path. Anat.* **283**:304, 1932.

The anomaly occurred in a new-born girl with multiple malformations, and consisted in rudimentary development of the epiglottis. In place of the latter was a group of cartilaginous nodules.

O. T. SCHULTZ.

TUBERCULOSIS OF BONE, ESPECIALLY OF THE SKULL. J. ERDHEIM, *Virchows Arch. f. path. Anat.* **283**:354, 1932.

Erdheim begins his fifty-nine page dissertation with the statement that tuberculosis of bone has not received the careful attention by general pathologists that its importance warrants. He then presents a histologic study of a case of tuberculosis of the skull, building a word picture of the dynamics of the process from beginning to end. In the skull, the course of events can be much more clearly traced than in other bones. In the zone of active progressive involvement, typical miliary and conglomerate tubercles are formed in the marrow spaces. The tuberculous granulation tissue causes lacunar resorption of the bone by pressure. Caseation leads to necrosis of the granulation tissue and of bone that has not been resorbed. The area of earliest destruction, after it breaks through the outer table, leads to the formation of a tuberculous cavity. Peripheral to the advancing zone, the bone undergoes osteosclerosis, characterized by fibrosis of the marrow tissue and by deposition of new bone on the surface of the original trabeculae. This reaction, which Erdheim terms paratuberculous, is due to tuberculotoxic substances

that diffuse out into the tissue. It is seen also in the pericranium and scalp and in the dura, when the tuberculous process approaches these structures. The paratuberculous zone is in turn invaded and eroded by the advancing process. The destructiveness of the latter is greater in the diploe than in the outer table, and it is greater in the inner table than in the diploe, because the process spreads along the outer surface of the dura. Because of the undermining of the outer table by destruction of the diploe and because of the still greater destruction of the inner table, the defect of the inner table is much larger than that of the outer table. Anatomically, this condition is characteristic of tuberculosis of the skull, and its roentgenologic detection should establish the diagnosis. The clinical diagnosis in the case studied was gumma of the skull, and the patient had received antisiphilitic treatment for two years. Erdheim maintains that the correct diagnosis should have been made from the roentgenogram, and states that he made the diagnosis of tuberculosis from the verbal description even before he had seen the specimen. As the process extends peripherally, healing may take place in the wall of the original cavity. The latter may be partly epithelialized by the downgrowth of the epidermis of the scalp; a fibrous connective tissue membrane is formed, and beneath this new bone formation may occur. The new bone may be primitive blue bone, its primitive character being the result of the action of diffusible tuberculotoxin. In the outer table, the osteosclerotic process that precedes destruction leads to smooth thickening of the outer surface; in the inner table, it leads to osteophytic thickening of the inner surface. Spread of the process within the diploe may lead to the formation of secondary cavities that break through the outer table and form sinuses through the scalp. The floor of the original cavity is formed by the thickened dura, the thickening being due to tuberculous pachymeningitis externa and interna. The pia-arachnoid becomes adherent to the internal surface of the dura. Progressive erosion of the dura leads finally to abscess of the brain. The brain lesion may be tuberculous or may be due to secondary invaders of the cavity. Although reparative processes in the older portions of the tuberculous area of the skull may lead to apparent healing, recidivation usually occurs.

O. T. SCHULTZ.

CHOLESTEROL PLEURITIS AND PERICARDITIS. G. DÁNIEL and S. PUDER, *Virchows Arch. f. path. Anat.* **284**:853, 1932.

A man, aged 52, had contracted syphilis fifteen years before death. Five years before death he had pleuritis, since which time he had been in poor health. Two weeks before death a dry cough, dyspnea and extreme weakness developed. The Wassermann reaction was strongly positive, and a few tubercle bacilli were found in the sputum. The clinical diagnosis lay between gumma and tuberculosis of the left lung. Autopsy revealed a massive chyloform exudate in the pericardial and left pleural cavities and a smaller quantity of similar exudate in the right side of the thoracic cavity. The exudate contained cholesterol, fats and phosphatids. The involved serous membranes were chronically inflamed, the process being histologically nonspecific. The authors ascribe the character of the exudate to inspissation of an originally hemorrhagic purulent exudate. In the upper lobe of the left lung was a fibrous nodular area. Histologically it could not be definitely determined whether this was a gumma or a tuberculoma; the authors think it was a combination of the two processes. There was syphilitic aortitis. In the available literature the authors could find only two previously reported cases of cholesterol pericarditis.

O. T. SCHULTZ.

CONGENITAL FIBROUS MYOCARDITIS. C. FROBOESE, *Virchows Arch. f. path. Anat.* **284**:861, 1932.

The author gives a brief description and discussion of a case of fibrous myocarditis of the right ventricle in a girl 6 months old. There were no other cardiac abnormalities. He believes that the fibrotic process was the result of

infection, which occurred either in the first few weeks of life or before birth. The child had had an attack of dyspnea shortly after birth. The author inclines to the view that the process had its origin in intra-uterine life.

O. T. SCHULTZ.

ARTERIOLAR CHANGES IN CHRONIC NEPHRITIS. M. A. ZACHARJEWSKAJA.
Virchows Arch. f. path. Anat. **284**:890, 1932.

The author reports a histologic study of the arterioles of nineteen kidneys, undertaken for the purpose of determining the relation of arteriolar sclerosis and arteriolar necrosis to each other and to the severity of the nephritic process. The material is subdivided into acute, subacute and chronic glomerulonephritis (eight cases), nephrosis (two cases) and nephrosclerosis (nine cases). Obliterative endarteritis was noted in the arterioles that supplied fibrosed glomeruli. Arteriolar sclerosis was absent or slight in the kidneys in acute and subacute glomerulonephritis. The sclerosis bore no apparent relation to the degree of the inflammatory process present in the kidney. Necrosis of arterioles and glomeruli was not seen alone, but was observed only in association with arteriolar sclerosis, and usually with the more severe grades of the latter.

O. T. SCHULTZ.

Pathologic Chemistry and Physics

THE SPERMICIDAL POWERS OF CHEMICAL CONTRACEPTIVES. J. R. BAKER,
J. Hyg. **29**:323, 1930; **31**:189 and 309, 1931; **32**:171 and 550, 1932.

A comparative examination was made of the effectiveness for human and guinea-pig sperms of a large group of pure substances and commercial contraceptive preparations of known chemical composition. The conditions of the examination were so arranged as to approximate as nearly as possible in vitro the conditions and concentrations of the acting substances within the vagina. The killing concentration was determined for a series of pure substances, and it was found that the six having the greatest spermicidal power were quinones. In the hydroxy-benzenes and their derivatives, the relative positions of the hydroxyl groups were significant. Of the commercial pessaries tested with human sperms, those which contained butter of cocoa were less effective than those which did not. The effectiveness of foaming mixtures and of soaps is discussed. Human and guinea-pig sperms were susceptible to the substances tested in almost the same degree. Evidence is presented for the existence in human semen of a substance which protects both human and guinea-pig sperms against some spermaticides, especially sodium oleate, vanillin and potassium borotartrate.

L. E. SHINN.

THE COMPOSITION OF THE LIPOIDS IN NORMAL AND PATHOLOGIC ORGANS. B. LUSTIG and E. MANDLER, Biochem. Ztschr. **249**:352 and 366, 1932.

The lipid content of two normal, two carcinomatous and one melanosarcomatous liver was examined. Two fractions were distinguished, one which could be directly extracted and a second which was obtained after pepsin digestion (bound lipid). In the carcinoma extracts, the phosphorus content was diminished. In the melanosarcoma extracts, normal values were found. The phosphorus content of the directly extractable carcinoma extracts corresponds with the phosphorus content of the substances precipitable with acetone, while in the melanosarcoma extract, only a part of the phosphorus-containing substances can be precipitated with acetone. The phosphatides precipitated with acetone in the carcinoma and sarcoma extracts show an increased phosphorus content in comparison with that in normal livers. The acid number of the sarcoma extracts was markedly increased, with simultaneous elevation of the ester number. The amount of the nonsaponifiable lipid and of the cholesterol was increased in the directly extractable lipoids of the

carcinoma and sarcoma extracts, but decreased in the bound lipid of the melanoma. In the bound lipid, a decrease of the phosphorus content was observed in carcinoma and sarcoma extracts. The amount of the nonsaponifiable material was increased in the carcinoma and diminished in the sarcoma extracts. The amount of free fatty acids was increased in the melanoma extracts in contrast with the carcinoma extracts.

WILHELM C. HUEPER.

MITOGENETIC RADIATION OF LEUKOCYTES. JACOB KLENIZKY, *Biochem. Ztschr.* **252**:126, 1932.

Leukocytes emit mitogenetic rays. The spectral analysis of the rays shows bands which are characteristic for glycolysis, oxidation and phosphatase action. There are also bands which are probably due to proteolysis. The quality to emit rays is mainly an intracellular factor. Cell-free exudates show only traces of a glycolytic radiation.

WILHELM C. HUEPER.

STAPHYLOCOCCIC STONES OF THE KIDNEYS. K. BOSHAMER, *München. med. Wchnschr.* **79**:1951, 1932.

Staphylococcic stones are found primarily in nephritis from various causes, and they are regarded as formed by the precipitation of the proteins of exudates, diluted by the urine, with the bacteria present. This precipitate forms the kernel of the stone around which further deposits of protein, bacteria and inorganic salts collect.

D. O. ROSBASH.

EFFECT OF X-RAYS ON BONE MARROW. ANNIBALE CASATI, *Strahlentherapie* **43**:582, 1932.

After intensive irradiation of the bone marrow, two phases occur, a degenerative and a regenerative one. During the degenerative phase, the parenchyma cells of the marrow are transformed into connective tissue cells. During the reparatory phase, these cells become again parenchyma cells.

WILHELM C. HUEPER.

EFFECT OF X-RAYS ON CALCIUM AND POTASSIUM METABOLISM. K. ADLER and OTTO WIEDERHOLD, *Strahlentherapie* **44**:383, 1932.

After large doses of x-rays, a decrease in the potassium and calcium content of the blood serum of rabbits was found. The calcium level decreased by 34.49 per cent and the potassium content by 25.2 per cent. Parallel changes were observed in the calcium and potassium content of the skin after irradiation.

WILHELM C. HUEPER.

ANATOMY OF TUBERCULOUS INFECTION IN MONGOLS. W. STEFKO, *Virchows Arch. f. path. Anat.* **283**:99, 1932.

Stefko presents a study of tuberculosis as seen in 131 Mongols. From the context it appears that the Mongols were Siberians resident in Russia at the time of death. On gross anatomic grounds Stefko divides tuberculosis, as encountered in his material, into four types: (1) disseminated primary disease of the lung with early involvement of the vessels and secondary involvement of the serous cavities; (2) rapid progress of the process from the primary focus; (3) exacerbation of the primary focus with caseous pneumonia and generalization; (4) primary tuberculosis of the intestine with secondary generalization. He gives the gross and microscopic findings in a characteristic example of each type. Infection began as a bronchiolitis and peribronchiolitis, which spread rapidly and destroyed the local blood vessels. It was then disseminated throughout the lung. Hemorrhage was an early frequent manifestation. The characteristics of the

initial stages are ascribed to structural peculiarities of the bronchial system, which Stefko promises to describe in another communication. He also postulates peculiarities in the structure of the pulmonary vessels that render the latter more susceptible to the destructive action of the infection. In every instance, the tuberculosis was of the infantile or adolescent type. There is a general discussion of the relationship of race and tuberculosis and of the effect of racial constitution and immunity on the course of the infection.

O. T. SCHULTZ.

Microbiology and Parasitology

THE INFLUENCE OF INORGANIC SALTS ON THE MULTIPLICATION OF GONOCOCCUS.

C. P. MILLER, JR., A. B. HASTINGS and R. CASTLES, *J. Bact.* **24**:439, 1932.

Sodium and potassium were found to be interchangeable and nontoxic at high concentration. Calcium and magnesium were unessential but inhibited growth at concentrations greater than 30 millimols per liter. Citrate and oxalate nullified the toxic action of calcium but not that of magnesium. Growth occurred between p_H 6 and 8.2, with optimum growth at from p_H 7 to 7.6. Unless the medium was well buffered either with bicarbonate or with phosphate, growth did not occur. Chloride was replaceable by nitrate or sulphate without impairing growth. Below salt concentrations of 150 and above 550 millimols per liter, growth was inhibited.

FROM AUTHORS' SUMMARY.

HISTOLOGIC CHANGES IN THE BRAIN IN SPOTTED FEVER OF GUINEA-PIGS.

MAKATO KODAMA and KENSABURO TAKAHASHI, *Zentralbl. f. Bakt. (Abt. 1)* **121**:32, 1931.

The authors studied the brains of eighty-six guinea-pigs infected intracardially or intraperitoneally with the virus of spotted fever and examined within two weeks after the termination of the febrile period. In every brain small nodules of glia cells were found, especially (80 per cent) in the gray matter of the cerebral cortex. The authors conclude, therefore, that the four diagnostic points of value in spotted fever of guinea-pigs are: fever, loss of weight, monocytosis and nodules in the brain.

PAUL R. CANNON.

MONOCYTOSIS IN SPOTTED FEVER OF GUINEA-PIGS. MICHIO KONO, *Zentralbl. f. Bakt. (Abt. 1)* **121**:37, 1931.

Differential blood smears were made from fifteen guinea-pigs infected with spotted fever and from nine healthy controls. During the febrile period there were leukocytosis and lymphopenia. The outstanding feature during the febrile period, in all instances, was the presence of large monocytes, reaching from two to five times the normal number.

PAUL R. CANNON.

YELLOW FEVER IN WHITE MICE. J. E. DINGER, *Zentralbl. f. Bakt. (Abt. 1)* **121**:194, 1931.

The author has confirmed and extended the observations of Theiler concerning the effects of the yellow fever virus in mice. The intracerebral injection of the virus into white mice caused fatal yellow fever in 100 per cent of the cases, the mice usually dying in from six to eight days with acute encephalitis, with hemorrhages in the stomach, fatty changes in the liver and swelling of the suprarenals and lymph nodes. No specific nuclear inclusions could be found in the ganglion cells.

The virus in the mouse was neurotropic and could not be found during the course of the infection in the blood, spleen, liver or kidneys. It was found, however, in the suprarenals. When emulsions of brain from infected mice were injected into rhesus monkeys, the virus could be recovered from the blood of the latter. Mice could be infected by subcutaneous, intraperitoneal and intramuscular injections

of the virus, but the fatality rate was less and the survival time longer than in the intracerebrally inoculated animals. Survivors were immune to reinjections of the virus.

The virus from the brains of mice was filtrable, and when fed to mosquitoes (*Aedes aegypti*) was transmitted to monkeys twenty-six days later, both by bites of the mosquitoes and by injection of an emulsion of the infected mosquitoes.

PAUL R. CANNON.

BACTERIOLOGY OF THE SPUTUM OF ASTHMATIC PERSONS. W. STORM VAN LEEUWEN and A. J. STORM VAN LEEUWEN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **76**:109, 1932.

The bacterial flora was studied in the sputum of two groups of asthmatic persons: (1) those whose asthma was caused by house allergens and (2) those whose asthma was bronchitic. The symptoms of patients in the first group disappear in allergen-free chambers. The patients of the second group do not benefit by the foregoing treatment and show no specific skin sensitiveness to any known allergens. No characteristic qualitative or quantitative differences were noted in the bacteria in smears and in cultures. Comparison of the bacteriologic results with skin sensitiveness to bacterial vaccines brought only negative results. The authors conclude that there is no evidence of direct relation between the bacteria of the sputum and the allergic condition. It could not be excluded that the bacterial invasion prepares the ground for allergic sensitization or that it lowers the threshold for the allergens, and so is instrumental in bringing about the asthmatic attack.

I. DAVIDSOHN.

ORIGIN OF BACTERIOPHAGE IN ANIMALS. F. HODER and M. HREBELIANOVICH, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **76**:141, 1933.

The bacteriophage found in the stools of guinea-pigs after they had been fed bacterial cultures did not originate within the animal body but was introduced with the cultures. It could always be found in a large amount in the culture before its introduction into the animal. It was directed, as a rule, against heterologous bacteria and was found in the excretion of the guinea-pigs only following the feeding of lysinogenic bacterial species. The great variations in the content of bacteriophage in the cultures was due to a great extent to changes in the sensitiveness of bacteria to the bacteriophage.

I. DAVIDSOHN.

TUBERCULOUS BACILLURIA. S. BADER, *Ztschr. f. Tuberk.* **65**:202, 1932.

The urine of a hundred patients with severe pulmonary tuberculosis was examined for the presence of tubercle bacilli. Only in five cases in which urogenital tuberculosis complicated the pulmonary disease were tubercle bacilli found.

VIRULENCE OF TUBERCLE BACILLI FROM THE BLOOD IN ACUTE POLYARTHRITIS. GIAN CARLO TORRI, *Ztschr. f. Tuberk.* **66**:129, 1932.

The recovery of acid-fast bacilli from the blood stream is difficult to interpret if identification is based on smears of sediments and cultural methods alone, as typical apathogenic acid-fast bacilli have been isolated even from normal persons. The author therefore investigated the pathogenicity of ten strains of acid-fast rods isolated by Löwestein's method from nine cases of acute polyarthritis and one of exudative pleurisy. Two-tenths cubic centimeter of a triturated 2 cc. saline suspension of a loopful of each of these cultures was injected subcutaneously into guinea-pigs and intravenously into rabbits and chickens. Nine strains proved to be pathogenic for guinea-pigs, seven for rabbits and two for chickens. Three strains were incontestably human tubercle bacilli. The patients these were isolated

from were all reactors to tuberculin, and two had a pulmonary pathologic process. Five strains were probably avian tubercle bacilli. The relationship of tubercle bacilleemia to acute polyarthritis is still unelucidated.

AARON EDWIN MARGULIS.

NORMAL DEVELOPMENT OF TRANSMIGRATION CULTURES OF *BACILLUS COLI*.
GUNNAR FISCHER, *Acta path. et microbiol. Scandinav. supp.* 9, 1932.

Fischer introduces the term "transmigration culture" (*Transmigrationskultur*) to designate the growth of motile bacteria in semisolid agar. The phenomena manifested by bacteria growing in such medium were first described by Wassén and by Dimitrijevic independently. Fischer reports in great detail his observations on the growth of *B. coli*. Long test tubes containing 0.2 per cent agar with 2 per cent peptone were used. Single cell cultures of typical and thoroughly studied strains were employed. The characteristic phenomena of the transmigration cultures were due to the motility of the micro-organisms.

After the test tubes of culture mediums were inoculated, a certain time elapsed during which a growth developed on the surface, and then changes took place in the depth of the medium which occurred with striking regularity and which could be assigned to three groups: the formation of a veil, of one ring and of two rings. All of these formations grew down into the medium and moved through its entire length till they reached the bottom and then disappeared. Behind the rings a zone of clear agar developed.

These growth phenomena developed and moved through the medium according to a definite schedule. As a rule, each strain formed only one type of transmigration growth, but under certain experimental conditions some strains were able to produce all three types. Similar phenomena were observed when the medium was placed in Petri dishes. Here the veil and the rings moved from the inoculated center toward the periphery. However, test tubes proved more satisfactory for the purposes of study. A microscopic study revealed that the rings and the veil were due to accumulations of bacteria, and that the clear zone behind the rings was due to greatly diminished numbers of bacteria. The lower ring, which was the wider of the two, consisted of bacilli measuring from 2 to 7 microns; it displayed an active and characteristic motility, which differed both in speed and in form from the motility of the shorter and narrower bacilli, the accumulation of which formed the upper ring. Above the upper ring the bacilli gradually became shorter and narrower, and lost their motility. In the cultures in which only one ring was seen, microscopic examination showed the presence of an accumulation of the shorter variety of bacilli. The accumulation was not sufficiently dense to be seen with the naked eye. Also, in cultures with veil formation, the microscope revealed a roughly similar distribution of the morphologically different bacilli in the various levels.

All these forms were also found in broth cultures of *B. coli*, but here they were found in different levels of the test tubes. The bacilli of the lower ring were actively multiplying and were in the logarithmic phase of growth; those of the upper ring were in the phase of negative acceleration, and the bacilli found above both rings were in the maximum stationary phase. The bacilli did not move in any definite direction; their downward motion was the result of a bacteriolytic process taking place at the posterior border of the rings. The anterior border of the ring was perfectly smooth. That was due to differences in surface tension. A certain minimum of nutritive substances was necessary for the development of the cultures. The amount of nutrition determined the speed of the downgrowth. The hydrogen ion concentration, which permitted the development of the culture, ranged from 5.3 to 9.5, with an optimum pH of 7. The highest concentration of agar which still permitted a downgrowth was 0.5 per cent. The lower the concentration, the faster was the downgrowth. The agar which was passed by the bacteria in their downward growth permitted only a scanty growth of new implants. The inhibition was due to a thermostable and filtrable toxic substance which was neither

strain-specific nor species-specific. It appeared during the third hour after the inoculation of the medium and was the reason for the termination of the logarithmic phase of the bacterial growth. The used culture medium regained some of its ability to promote growth of bacteria by dilution with distilled water or with plain agar. The effect of the latter depended on the dilution of the toxic substance.

Fischer believes that the toxic substance may be related to, or identical with, the antiviral of Besredka. The bacteriolysis observed behind the rings was due to the lytic agent, which dissolved the motile young bacilli, but did not damage the older, nonmotile forms. The lytic agent has qualities like those of the toxic substance; it differs from the bacteriophage and is not due to microbial dissociation.

In the last chapter some bacteria are listed according to their ability in forming transmigration cultures.

I. DAVIDSOHN.

ACUTE TUBERCULOUS SEPSIS. F. SALTZMAN, *Finska läk.-sällsk. handl.* **74**:588, 1932.

Reports of seven cases of acute tuberculous sepsis were found in the literature. A new case, fatal after a short course, is reported. Numerous necroses with many bacilli but without tubercles and giant cells were present in the lymph glands, the spleen, the liver and other internal organs. The place of entrance of the infection was not found. There were no old tuberculous foci in the body.

Immunology

SEROLOGICAL STUDIES ON IODINATED SERUM. J. JACOBS, *J. Immunol.* **23**:361 and 375, 1932.

When iodine is added to animal serums without the presence of acid or alkali, substances are formed which precipitate with antisera prepared from iodinated serums. This change takes place in the presence of aqueous solutions as dilute as thirty-second normal. Wormall's observation that *di*-iodotyrosine, but not potassium iodide, inhibits precipitation specifically in systems of iodinated proteins and their antisera was confirmed. The specificity of substances formed in serums iodinated in neutral solutions was tested in several ways. Their specificity is similar to that of other iodinated proteins.

Further evidence of guinea-pig sensitization to compound solution of iodine and guinea-pig serum preparations is described. A much stronger specific sensitization is produced by compound solution of iodine and horse serum preparations. Animals sensitized by these methods are more or less equally susceptible to shock by iodinated guinea-pig and iodinated foreign serums. Evidence is presented which indicates that *di*-iodotyrosine, but not ionic iodine, inhibits shock in these anaphylactic systems.

AUTHOR'S SUMMARIES.

ANTIGENIC SUBSTANCES IN S AND R TUBERCLE BACILLI. C. E. RICE and G. B. REED, *J. Immunol.* **23**:385, 1932.

The S type of various strains of acid-fast bacteria, *Mycobacterium leprae* and human, bovine and avian tubercle bacilli has been found to contain antigenic substances not present in the R type of the same strains, dissociation apparently being accompanied by a considerable loss in antigenic complexity. Immune sera prepared against such S organisms contain certain antibodies reacting with extracts of the homologous S organisms but not with the homologous R type, other antibodies reacting with both S and R types of the same species and a third type of antibody detected by antigens prepared from the other species of acid-fast bacteria, that is, a group antibody. Antisera prepared against R organisms, on the other hand, appear to lack the S-specific antibody which is found in S antiserum, but contain a much higher proportion of antibodies reacting with extracts prepared from other acid-fast species. The possible chemical nature of the various antigenic substances has been briefly discussed.

AUTHORS' SUMMARY.

ACTIVE IMMUNIZATION OF WHITE MICE BY A NON-POLYSACCHARIDE AND PROBABLY NON-PROTEIN DERIVATIVE OF THE PNEUMOCOCCUS. L. D. FELTON, *J. Immunol.* **23**:405, 1932.

White mice may be immunized with a fraction of pneumococcus which is soluble in copper acetate in the presence of saturated sodium chloride, and may be extracted with alcohol from the dried copper-free filtrate. This antigen gives a negative Molisch reaction and is probably free from protein. Also no precipitation occurs with antipneumococcus horse serum. The soluble carbohydrates of Avery and Heidelberger in proper dosage prevent the immunizing effect of this antigen. The immunizing antigen has been extracted by the copper method from samples of both type I and type II polysaccharides. Demonstrable immunity is developed in seventy-two hours after intraperitoneal injection and in a shorter time following intravenous injection. Immunity after a single injection of antigen remains maximal for at least three weeks. The immunity conferred on white mice from a single injection is type specific.

AUTHOR'S SUMMARY.

A QUANTITATIVE STUDY OF THE PRECIPITIN REACTION WITH SPECIAL REFERENCE TO CRYSTALLINE EGG ALBUMIN AND ITS ANTIBODY. J. T. CULBERTSON, *J. Immunol.* **23**:439, 1932.

A method has been described to find the amount of precipitable antibody in a unit volume of rabbit anticrystalline egg albumin serum by the determination of the amount of antigen necessary to neutralize the precipitin of a small volume of the antiserum. At the neutralization point, antigen and antibody combine in a constant ratio to give the maximum precipitate obtainable from the antiserum. Neither precipitinogen nor precipitin remains in the supernatant fluid over the precipitate at the neutralization point. The results obtained by this method are identical with the results obtained by the micro-analytic method for estimating the precipitin content of an antiserum to crystalline egg albumin. The method has proved useful for the accurate determination of the precipitable antibody contained in such an antiserum, especially when only a limited amount of antiserum is available. The quantitative method proposed has been compared with the antigen dilution method and with the antiserum dilution method by the titration of thirty-four antisera to crystalline egg albumin by the three methods. The results offered indicate that the antigen dilution method, widely used in the titration of precipitating antisera, is not a satisfactory method to evaluate anticrystalline egg albumin sera according to the amount of antibody contained. Fair correlation is noted between the results of the antiserum dilution method and the results of the quantitative "neutralization" method described here. The neutralization method results in a more exact titer than that arrived at by the antiserum dilution method, since the quantitative method establishes the absolute amount by weight in milligrams of the precipitable antibody contained per cubic centimeter of antiserum. The quantitative method which we have described for the titration of antisera to crystalline egg albumin is not satisfactory for the titration of antisera to horse serum.

AUTHOR'S SUMMARY.

A SPECIFIC REACTION OF CONVALESCENT SERUM ON STREPTOCOCCUS FROM POLIOMYELITIS. E. C. ROSENOW, *J. Immunol.* **23**:455, 1932.

By studying the effect of convalescent serum on streptococci with characteristic cataphoretic velocity, isolated in cases of poliomyelitis, a marked and specific slowing or charge-reducing effect has been discovered. This action of the serum increases during recovery from poliomyelitis, and is at its maximum during the fourth week after the onset of the acute attack, following which it gradually diminishes, but remains readily demonstrable even twenty years after recovery. The reaction is specific, in that the serum of persons and monkeys that have recovered from typical attacks affects the strains both from human beings and from monkeys, in that streptococci and bacteria from other sources than polio-

myelitis are not affected, and in that the reacting antibodies can be removed by absorption only with the streptococcus from poliomyelitis. The results indicate that the streptococcus consistently isolated in poliomyelitis is not a contamination or an agonal or postmortem invader.

AUTHOR'S SUMMARY.

THE HYPOTHETICAL INCORPORATION OF INJECTED ANTIGEN IN RESULTING ANTIBODY. S. B. HOOKER and W. C. BOYD, *J. Immunol.* **23**:465, 1932.

From the quantitative interrelations of an immune serum prepared by the injection of an arsenic-containing diazo-protein, and as test antigen, a heterologous arsenic-containing diazo-protein, we calculate conservatively that the buchnerian hypothesis, which claims antibody to be a conjugate of injected antigen and body globulin, demands the presence of at least 2.5 and more probably 2,500 times as much arsenic in the immune serum as could possibly be there according to the testimony of direct quantitative chemical tests. The number of chemically defined groups (haptens) entering the molecule during the preparation of a synthetic diazo-protein is determined and shown to agree with the theoretical number. The proportion of protein-combined haptens necessary for visible specific precipitation is approximated for one antigen-antibody system. A suggestion is given as to the number of specific combining groups (antihaptens) in one molecule of the antibody in question.

AUTHORS' SUMMARY.

THE RETICULO-ENDOTHELIAL SYSTEM AND THE SOURCE OF OPSONIN. A. R. ELVIDGE, *J. Immunol.* **24**:31, 1933.

It is concluded that opsonin production is a function of cells of the reticulo-endothelial system, and that opsonin is a definite chemical substance.

AUTHOR'S SUMMARY.

THE ALLERGIC VERSUS THE TOXIN-ANTITOXIN HYPOTHESIS OF SCARLET FEVER. S. B. HOOKER, *J. Immunol.* **24**:65, 1933.

The objections to the toxin-antitoxin hypothesis and the arguments in favor of the substituted allergic interpretation are not considered well founded. In addition, it should be borne in mind that although resistance may be sometimes independent of allergy, there is a mass of evidence showing that allergic (specific) inflammation delays bacterial invasion and hastens healing. The allergic cutaneous response is a local expression of the generally enhanced capacity for an unusually rapid development of specific resistance. It is, in general, much more an index of immunity than of susceptibility; the Dick reaction is surely not an index of immunity and so improbably is of an allergic nature. Further, a brief incubation period is characteristic of typical scarlet fever as well as of diphtheria, bacillary dysentery and other diseases the pathogenesis of which rests mainly on the toxigenic property of their incitants. Finally, although there are examples of what may be termed "immunologic" diseases, such as hay fever, the specific antibody concerned somehow in the production of symptoms is not capable of neutralizing the active substance of the extraneous incitant. The neutralizing property of scarlatinal antitoxin is unquestioned. The allergic hypothesis embodies the unattractive and unnecessary conception that both the symptoms and the cure of the disease are mediated by the same neutralizing antibody.

AUTHOR'S SUMMARY.

LOCAL CUTANEOUS SENSITIZATION BY THE PROTEIN OF TUBERCULIN. F. B. SEIBERT, *J. Infect. Dis.* **51**:383, 1932.

Specific cutaneous sensitization can be produced in normal rabbits and guinea-pigs by repeated injections of the highly purified, undenatured protein of tuberculin. This sensitization is of as high degree, and is of the same type, as that

produced by infection with live tubercle bacilli or by injection of dead bacilli. The most successful methods for preparing and purifying the protein of tuberculin in such a way as to preserve its antigenic capacity were precipitation by means of ammonium sulphate or trichloroacetic acid and mere concentration and washing by means of ultrafiltration.

AUTHOR'S SUMMARY.

PRECIPITIN REACTION: EFFECT OF ELECTROLYTES. C. M. DOWNS and S. GOTTLIEB, *J. Infect. Dis.* **51**:460, 1932.

Certain salts in molar solution inhibit the formation of a precipitate from horse serum and rabbit antihorse serum, but others do not. All the salts studied inhibit the formation of a precipitate from crystalline egg albumin and its antiserum when present in molar solution. The addition of salts does not induce the formation of a precipitate in concentrations of antigen and antibody that fail to give precipitates in the absence of these salts. The washed specific precipitates are soluble in dilute solutions of weak or strong acids and alkalis, and these solubilities are independent of the salt present at the formation of the precipitates. A precipitate when once formed in a dilute solution of a given salt is not soluble in a molar solution of the same salt even though this molar solution can serve originally to inhibit the formation of the precipitate.

AUTHORS' SUMMARY.

ANTIGENIC PROPERTIES OF THE VIRUS OF RABIES. L. C. HAVENS and C. R. MAYFIELD, *J. Infect. Dis.* **51**:511, 1932.

Rabies virus possesses the property of absorbing the specific antibodies from immune rabies serum. Agglutinin-absorption experiments with nine strains and their homologous serums indicate that differences in antigenic composition exist between strains of this virus. The antigenic dissimilarity shown by agglutinin absorption was confirmed by neutralization experiments. There appears to be at least one component which is possessed by all of these nine strains. The differences observed seem to be due to the presence or absence, in whole or in part, of additional antigenic factors.

AUTHORS' SUMMARY.

LATENT PERIOD IN PASSIVE ANAPHYLAXIS. J. H. LEWIS, *J. Infect. Dis.* **51**:519, 1932.

The experiments of Friedberger, indicating that the latent period in passive anaphylaxis could be dispensed with by using a homologous sensitizing antiserum, could not be confirmed. With the use of a guinea-pig antituberculo-protein serum of high titer, guinea-pigs can be passively sensitized to a fatal anaphylactic death in not less than four hours after the injection of the sensitizing serum, the same period required for sensitization with a heterologous antiserum. The smooth muscle of the guinea-pig uterus will show anaphylactic sensitization two hours after an intravenous injection of homologous sensitizing serum. An isolated guinea-pig uterus is passively sensitized after remaining in a solution of guinea-pig antituberculo-protein serum for two hours. The uterus is not sensitized after four hours in a solution of rabbit antihorse serum.

AUTHOR'S SUMMARY.

SKIN REACTIVITY TO BACTERIAL FILTRATES. G. SHWARTZMAN, *J. Infect. Dis.* **51**:552, 1932.

There exist considerable differences in the neutralizability of meningococcus toxins obtained from various strains of the same serologic groups. The passage of strains of the meningococcus through mediums containing human blood lowers the neutralizability of their toxins by antistock serums. It is suggested that

attempts be made to obtain for therapeutic purposes serums that will neutralize satisfactorily the toxins of strains that have been passed through mediums containing human blood.

AUTHOR'S SUMMARY.

ANTIVIRUS ACTION OF POLIOMYELITIS SERUM. B. F. HOWITT, *J. Infect. Dis.* **51**: 565, 1932.

Of the serums from twenty-two treated patients who had recovered from poliomyelitis, six (27.2 per cent) gave positive in vitro neutralization of poliomyelitis virus, two (9 per cent) gave partial protection in the monkey and fourteen (63.6 per cent) conferred no protection. Of the serums from twenty untreated patients, eight (40 per cent) showed positive neutralization, one (5 per cent) gave partial protection and eleven (55 per cent) failed to neutralize the virus. Antivirus substances may be present in a certain percentage of treated persons, but apparently those receiving serum treatment show less tendency to produce neutralizing substances than the untreated ones. The patients showing complete recovery after transient or only slight paralysis give more evidence of the production of a potent serum than those in whom severe paralysis develops. The results of these experiments may aid in explaining certain discrepancies in the reports on human convalescent serum therapy in poliomyelitis, and certainly show the need for giving serum from known tested donors, either recovered or naturally immune to the disease. The use of a standardized serum from immunized large animals is indicated.

AUTHOR'S SUMMARY.

PASSIVE IMMUNITY TO CYSTICERCUS FASCIOLARIS IN THE ALBINO RAT. H. M. MILLER, JR., and M. L. GARDINER, *J. Prev. Med.* **6**:479, 1932.

Passive immunity to infection by a metazoan parasite has been demonstrated. Rats have been protected against infection with *Cysticercus fasciolaris*, the larval stage of *Taenia taeniaeformis*, by intraperitoneal injections of serum from infected rats or from those actively immunized against this worm. In these experiments serum from infected rats was more effective than that obtained from actively immunized individuals. Serum from rabbits given similar injections of worm material had but slight protective properties. A preliminary attempt to remove the active principle from immune serum was not successful. One cubic centimeter of immune serum per four hundred grams of rat body weight, the highest dilution used, was effective in inhibiting the development of cysts in three of four rats. Complete immunity persisted for twenty-six days, and in two of four rats for thirty-six days, after the injection of immune serum.

AUTHORS' SUMMARY.

THE PHAGOCYTIC FUNCTION OF LEUCOCYTES IN ANAEMIA. F. A. KNOTT and S. J. HARTFALL, *J. Path. & Bact.* **35**:889, 1932.

The functional activity of leukocytes (phagocytic power) has been estimated in cases of anemia of the anhematopoietic group. In pernicious anemia there is a marked lowering of this function in the stages of severe relapse, with improvement during recovery, but the phagocytic index rarely rises to the normal level. Estimation of the phagocytic power in cases complicated by sepsis has a prognostic value. There is marked depression in aplastic anemia. In simple achlorhydric anemia, even when the degree of anemia is severe, the leukocyte function is much less severely disturbed.

AUTHORS' SUMMARY.

SOME PROPERTIES OF DIPHTHERIA ANTITOXIN IN THE SERA OF ANIMALS OF DIFFERENT SPECIES. M. BARR, *J. Path. & Bact.* **35**:913, 1932.

Great variations were encountered between the salting-out limits, under the same conditions, of diphtheria antitoxin from serums obtained from actively immunized animals of different species. A considerable proportion of antitoxin

was found to be associated with the euglobulin (water-insoluble) fraction of most serums, particularly goose, rat and cow serums, all of which contained more than one quarter of the total antitoxin in the insoluble fraction. The highest proportion of antitoxin detected in this fraction of horse serum was 2.67 per cent of the total amount; the proportion was increased by the addition before dialysis of normal euglobulin free from antitoxin. The distribution of antitoxin between the two globulin fractions of horse serum bore no relation to the *in vivo/in vitro* ratio. The antitoxin contained in goose and rat serums was of extremely poor avidity, but a number of other serums showed normal avidity as judged by the value of the dilution ratio. Although guinea-pig and rat serums gave typical toxin-antitoxin flocculations, no satisfactory flocculation was obtained with serums from animals of other species.

AUTHOR'S SUMMARY.

THE PRODUCTION OF IMMUNITY TO VACCINIA VIRUS. R. W. FAIRBROTHER, *J. Path. & Bact.* **36**:55, 1933.

A high degree of immunity may follow the intracerebral inoculation of mixtures of immune serum and virus inactive on intradermal inoculation. Immune blood has a more marked action on the virus than immune serum. The probable importance of phagocytosis is discussed.

AUTHOR'S SUMMARY.

OBSERVATIONS ON SALMONELLA AGGLUTINATION AND RELATED PHENOMENA. P. B. WHITE, *J. Path. & Bact.* **36**:65, 1933.

A description of the serologic behavior of p variants of *Salmonella typhosus*, *S. enteritidis* and *S. aertrycke* is given: These three variants are identical in somatic agglutinating and agglutinin-binding properties. The p form does not react with, or fix the agglutinins of, anti-R serums. The R form may or may not agglutinate considerably with anti-p serums; in any case these serums show little or no loss of homologous titer when treated with intact R bacilli. The special serologic properties of the p form, like those of the R form, depend on the presence of carbohydrate haptens. While R bacilli contain a certain amount of the p hapten, apparently in their deeper substance, p bacilli are to all intents devoid of the characteristic R hapten. This relation, indicated by precipitation tests, is supported by the results of agglutinin-fixation tests. It is concluded that the p form is essentially a loss variant of the R form. The properties of a protein (T) extracted from *Salmonella* bacilli by acid 75 per cent alcohol are also described: Under adequate conditions of extraction the antigen isolated is common to the *Salmonella* group. Its antibodies, which are quite distinct from those of ordinary S, R or p antisera, agglutinate alcohol-washed or autolysed R and p bacilli, but fail to clump alcohol-washed S bacilli or young living cultures. This agglutinative difference of the suspensions corresponds with their ability or inability to bind the agglutinins of anti-T serums. The T protein exhausts its antiserum of agglutinins for R and p bacilli. It seems that the T protein, unlike the Q protein previously described, is situated beneath the reactive surface of the living organism and is only exposed by erosion. It is believed that alcohol acidified with hydrochloric acid and variously diluted will prove a valuable reagent in the fractionation of bacterial proteins.

AUTHOR'S SUMMARY.

SPECIES IMMUNITY TO PNEUMOCOCCUS. H. B. DAY, *J. Path. & Bact.* **36**:77, 1933.

The serologic and immunologic type specificity of pneumococci is due to the presence of type-specific antigens. These are formed by virulent pneumococci during the active phase of their life. With the maturation of pneumococci in aging cultures, preceding obvious or microscopic signs of autolysis, there is formed in their bodies (and later liberated in the surrounding medium) a species antigen. Injection of this antigen in animals induces an active immunity to pneumococci generally; the serum of animals so treated confers a similar passive

immunity on injection. The species antigen appears to be a product of the type-specific antigen which is dissociated through the action of the pneumococcic enzymes into a free antigenic group and type-specific material (nonantigenic). The freed antigenic group is common to all virulent (S) pneumococci, and forms the species antigen. This hypothesis is supported by the following observations: The appearance of the species antigen coincides with the disappearance of the type-specific antigen. The injection of "degraded" (R) pneumococci which contain no type-specific antigen produces no sort of immunity. The reactions of the type-specific and the species antigen to such agents as heat acid and alkali are similar. There is direct quantitative correspondence between the amounts of type-specific and of species antigen needed to induce immunity to any given type of pneumococcus. It is possible to convert type-specific antigen into species antigen *in vitro*, through the action of pneumococcic enzymes.

AUTHOR'S SUMMARY.

AN ALLERGIC SKIN REACTION AFTER SCARLET FEVER. H. J. GIBSON and J. P. MCGIBBON, *Lancet* 2:729, 1932.

In a series of cases of scarlet fever weekly intracutaneous tests were carried out with an extract prepared from cultures of hemolytic streptococci representing the soluble intracellular products of the organisms freed from diffusible substances. A 1:100 dilution of the extract was used. Twenty-eight patients were examined, and in twenty-two the reaction, which was negative during the first week, became strongly positive by the fourth week. The allergic reaction developed in all patients over 7 years of age.

AUTHORS' SUMMARY.

LYSOZYME. A. FLEMING, *Proc. Roy. Soc. Med. (Sect. Path.)* 26:1, 1932.

The main points are: That lysozyme is a widely distributed antibacterial ferment which is probably inherent in all animal cells, and constitutes a primary method of destroying bacteria. That lysozyme, while acting most strikingly on nonpathogenic bacteria, can attack pathogenic organisms when allowed to act in the full strength in which it occurs in some parts of the body. That it is easy to make bacteria relatively resistant to lysozyme, so that any pathogenic microbe isolated from the body, where it has been growing in the presence of a non-lethal concentration of lysozyme, must have acquired increased resistance to the ferment. That there are some differences in the lysozyme of different tissues and in different animals whereby bacteria are susceptible to different lysozymes in varying degrees.

AUTHOR'S SUMMARY.

COLD AGGLUTINATION. I. T. MISAWA and T. OHTA, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 76:378, 1932.

The serum of a patient who suffered from syphilis and bronchial asthma, and who belonged to blood group AB, agglutinated at 0 C. the red cells of all four groups. By cooling the serum, a fine sediment was obtained, which agglutinated the red cells of the same person but not of other persons. It did not fix complement in the Wassermann reaction. The sediment was soluble in physiologic solution of sodium chloride at 37 C. The supernatant serum obtained after formation of the sediment agglutinated heterologous red cells and gave a positive Wassermann reaction. Heating for thirty minutes at 63 C. destroyed the cold agglutinins of the sediment. Sediments with similar qualities were obtained from normal bloods possessing cold agglutinins, when the blood was permitted to clot and the serum was separated at 37 C. An immune serum was produced in rabbits by injecting fresh cow's milk. Such serum contains cold agglutinins. A sediment was also obtained from such serum, using the procedure described. Its iso-agglutinins clumped red cells only at low temperatures.

I. DAVIDSOHN.

AUTOHEMOLYSINS IN PAROXYSMAL HEMOGLOBINURIA. T. MISAWA, T. OHTA and K. HEINO, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **76**:386, 1932.

Alcoholic extracts of human red cells of all four groups bind the autohemolysin at low temperatures, while alcoholic extracts of the bloods of the horse, ox and goat do not. Under the same condition human red cell extracts also remove the complement from the fresh serum of a patient with hemoglobinuria. At 37 C. the complement remains intact. Alcoholic extracts of the red cells of the ox, horse and sheep do not affect the complement, but extracts of hog red cells act similarly to those of human cells, owing to antigenic qualities which human and hog blood possess.

I. DAVIDSOHN.

RAPID PRECIPITATION REACTIONS WITH HETEROPHILIC ANTISERUMS. JOSEPH MUELLER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **76**:423, 1932.

Rapid precipitation occurred in mixtures of alcoholic extracts of heterophilic tissues and of specific antisera when proper dilutions of the extracts and proper concentrations of sodium chloride are employed. This was still further improved by the use of concentrated tissue extracts. Cholesterol did not improve the reactivity of the antigenic extracts. When nonconcentrated extracts were employed and the dilutions prepared with physiologic solution of sodium chloride, a precipitation with nonheterophilic sera was observed occasionally, while heterophilic sera did not react. That is due to greater instability of serum globulin in dilutions with low sodium chloride concentrations, while higher concentrations produce a greater stability. The heterophilic precipitate is finer and develops slower than the one observed in reactions between alcoholic tissue extracts and general lipoid antisera. On the other hand, heterophilic antisera react more markedly in complement fixation tests, possibly because complement fixation is an expression of a slow and invisible precipitation.

I. DAVIDSOHN.

EFFECT OF HYDROCHLORIC ACID AND OF SODIUM HYDROXIDE ON THE DIFFERENT MANIFESTATIONS OF THE ANTIBODY FUNCTION. GUISEPPE D'ALESSANDRO, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **76**:446, 1932.

When lipoid antisera, produced by injections of lecithin and of alcoholic extracts of horse kidneys, were mixed with proper concentrations of hydrochloric acid and of sodium hydroxide, the complement-fixing and hemolytic properties were destroyed, while the precipitating and agglutinating titers were increased. The required concentration of the acid or alkali is inversely proportionate to the temperature at which the reaction takes place. Other heterophilic antisera were influenced similarly to the two mentioned previously. Heterophilic immune sera, which commonly lack the ability to agglutinate the red cells of the guinea-pig, acquire this ability after treatment with hydrochloric acid. The addition of dextrose protects the hemolytic properties of the antiserum against the destructive effects of sodium hydroxide but not of hydrochloric acid.

I. DAVIDSOHN.

FORSSMAN ANTIGEN OF PNEUMOCOCCI. M. EISLER and A. HOWARD, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **76**:461, 1932.

The report of Bailey and Shorb concerning the finding of the Forssman antigen in pneumococci was confirmed. In the immune sera produced in rabbits with injections of the type I pneumococci there was no antibody against human red cells similar to the one which was produced by injections of *Bacillus dysenteriae* Shiga and of paratyphoid bacilli. The sheep hemolysin of the immune serum reacted with all types of pneumococci; it was therefore species-specific and not group-specific. *B. dysenteriae* Shiga and *B. paratyphosus* did not absorb the sheep lysin produced by the injection of pneumococci, and vice versa. The sheep lysin

was absorbed by the carbohydrate fraction of the pneumococci but not by their alcoholic extract. There was no relation between the amount of Forssman antigen present in the pneumococci and their virulence. An increase of the Forssman antigen was observed following growth on serum and ascites agar, but only in strains which were poor in antigen before, while a decrease was noted following growth in broth of strains with a high antigenic content. In broth to which saponin or sodium taurocholate were added, growth was very abundant, but the Forssman antigen of the bacteria invariably disappeared.

I. DAVIDSOHN.

SENSITIZATION TO PRODUCTS OF ONE'S OWN BODY. W. STORM VAN LEEUWEN and J. VAN NIEKERK, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **76**:479, 1932.

Oriel isolated from the urine of allergic patients a proteose, to which the skin of allergic persons reacted, while normal controls did not respond. Van Leeuwen and van Niekerk confirm these findings. In three cases a positive cutaneous reaction was obtained in the patients from whose urine the substance was isolated. It was recently suggested by Murphy and Lobe that the cutaneous reactions against human epithelium reported by van Leeuwen were due to histamine present in human skin. By experiments on a decerebrate cat, and by skin tests in allergic patients with histamine and with properly prepared extracts, the rôle of histamine was excluded.

I. DAVIDSOHN.

ORIGIN OF ANTIBODIES AGAINST LIPOID ANTIGENS AND THE NATURE OF THEIR SPECIFICITY. S. BERGEL, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **76**:484, 1932.

The lymphocytes are the origin of antibodies against lipoids. They produce a lipase-like, fat-splitting ferment. Bergel observed the development of agglutinins and of lysins against sheep red blood cells injected into the peritoneal cavities of mice. The product of the lymphocytes acts, at first, nonspecifically, but after repeated treatment with the same antigen, the lymphocytes produce a specific antibody. The peritoneal exudate of animals which were treated repeatedly with tubercle bacilli or with *Spirochaeta pallida* destroys the homologous antigen, but acts only feebly or not at all on other lipoids. In syphilis, antibodies are developed against the specific spirochetal lipoids and also against the general tissue lipoids.

I. DAVIDSOHN.

Tumors

MULTIPLE PRIMARY MALIGNANT TUMORS. S. WARREN and O. GATES, *Am. J. Cancer* **16**:1358, 1932.

The cases of multiple malignant tumors collected from the literature number 794. These, the 189 cases of Major, the 143 of Owen, the 93 of Ward and 40 of our own make a total of 1,259. In addition, 37 cases have been cited which we have been unable to verify. On the basis of all statistics, the frequency of multiple malignant tumors in cases of cancer is 1.84 per cent. On the basis of American statistics, the frequency is 3.9 per cent. In our own series of 1,078 autopsies on patients with cancer, the frequency is 3.7 per cent. The average duration from the onset of the earlier tumor to death in our cases is three years. Multiple cancers occur at approximately the same age as single ones. Multiple malignant tumors occur more frequently than can be explained on the basis of chance. Their occurrence may be explained by a predisposition or susceptibility to cancer in certain persons, or by the action of some factor favoring the development of malignancy. The nature of this predisposition is as yet unknown.

AUTHORS' SUMMARY.

ADENOLYMPHOMA (ONKOCYTOMA) OF THE PAROTID GLAND. R. H. JAFFÉ, *Am. J. Cancer* **16**:1415, 1932.

This paper deals with one of the rare adenolymphomatous tumors which occur in the region of the salivary glands. The epithelial lining of the glands is morphologically identical with a type of cell which develops physiologically in the salivary glands with progressing age and for which Hamperl has suggested the name "onkocytes." In the tumors the onkocytes display marked secretory activity, with the formation of intercellular secretion capillaries. This secretion leads to the formation of small cysts. The lymphatic tissue is not an essential part of the tumor, but is apparently the remnant of a lymph node.

AUTHOR'S SUMMARY.

THE TAR IN CIGARETTE SMOKE AND ITS POSSIBLE EFFECTS. WILLIAM D. McNALLY, *Am. J. Cancer* **16**:1502, 1932.

The tar of cigaret smoke contains nicotine, phenolic bodies, pyridine bases and ammonia, irritants which could account for "cigaret cough," the chronic bronchitis of the cigaret smoker, the leukoplakia in heavy smokers and the recorded increase of cancer of the lung. The temperature is not an important factor unless the cigaret is burned to the last centimeter, when the hot smoke becomes more irritating. With a tarry residue of from 4.84 to 15.29 per cent, a definite risk attaches to the smoking of a cigaret, especially since from 6.56 to 11.58 per cent may be absorbed or retained in the body. Cigarets should not be smoked too short, as the last 2 cm. retains most of the tar and other products of incomplete combustion.

AUTHOR'S SUMMARY.

THE ALLEGED CARCINOGENIC ACTION OF TOBACCO TAR. E. BOGAN and R. N. LOOMIS, *Am. J. Cancer* **16**:1515, 1932.

The results recorded indicate that "whatever carcinogenic properties may inhere in the use of tobacco, they cannot well be ascribed to the chemical effect of the tar derived from distillation of the tobacco."

SPINDLE-CELLED TUMOUR IN A FOWL FOLLOWING INJECTION OF 1:2:5:6-DIBENZANTHRACENE IN A FATTY MEDIUM. H. BURROWS, *Am. J. Cancer* **17**:1, 1933.

Bilateral spindle cell tumors appeared in one of two white Wyandotte hens at the sites of intramuscular and subcutaneous injections of 1-2-5-6-dibenzanthracene dissolved in lard. An autograft taken from one of these tumors became established and grew. There were metastases in the lung, liver and ovary. Attempts to transmit the tumor to six young chicks by grafting were not successful. A fowl given an injection only of lard as a control died very early in the course of the experiment.

AUTHOR'S SUMMARY.

CORRELATION OF X-RAY PICTURE WITH HISTOLOGY IN CERTAIN BREAST LESIONS. S. P. REIMANN and P. S. SEABOLD, *Am. J. Cancer* **17**:34, 1933.

Roentgenograms of female breasts were taken at intervals before, during and after menstruation and pregnancy. Fluctuations in the size of the breast tissue proper were found corresponding to these physiologic states. Two typical lesions of the breast were also studied in relation to the menstrual cycle, and were found to fluctuate in size with the stages of the process. These were periductal fibromas (adenofibroma, fibro-adenoma, etc.) and abnormal involution (chronic cystic mastitis, etc.). The lesions were removed surgically, and the histologic features were found to correspond to the theoretical condition for the time of removal in relation to menstruation. Attention to the menstrual phases and their different pictures is necessary for proper pathologic diagnosis of lesions of the breast. Incidentally, many of the names used for various pictures will then automatically

disappear. Ten patients with breasts "painful" just before the onset of the menstrual flow were treated with ovarian residue as recommended by Cutler. In six cases amelioration of the symptoms was obtained. Most patients with this symptom have "shotty" breasts. This can be recorded in the x-ray film, and in three cases thus far investigated in which the symptoms were relieved the "shottiness" was much reduced both to palpation and on films. It is not recommended that removal of doubtful lesions or of malignant tumors be delayed in order to take a series of x-ray films. X-ray films have advantages over transillumination as assistants in diagnosis. Fortunately, large, heavy breasts, which offer the greatest difficulties to palpation, give the clearest x-ray pictures. Also pathologic axillary and pectoral lymph nodes throw shadows, the significance of which will be discussed in another place.

AUTHORS' SUMMARY.

STUDIES ON THE HYDROGEN-ION CONCENTRATION OF THE BLOOD IN CANCER.
J. O. ELY, *Am. J. Cancer* **17**:58, 1933.

In cases of uncomplicated and untreated skin and superficial cancers the blood usually has a normal p_H . In uncomplicated cases of untreated and advanced internal cancers the blood usually has a p_H above normal. The blood of patients with benign tumors usually has a p_H above normal. In a number of pathologic conditions other than cancer the p_H of the blood is elevated as in cancer. In cases of cancer a p_H of the blood which is persistently high in spite of treatment appears to be a bad prognostic sign. The p_H of the blood by itself is of little, if any, diagnostic value in cancer.

AUTHOR'S SUMMARY.

INCIDENCE AND NATURE OF TUMORS IN CAPTIVE WILD MAMMALS AND BIRDS.
H. L. RATCLIFFE, *Am. J. Cancer* **17**:116, 1933.

The incidence of neoplasms in the orders and families of birds and mammals dying in the Philadelphia Zoological Gardens has shown little variation over a period of eleven years. In most orders and families the percentage of animals affected by tumor growth is proportional to the average period of exhibition of the group. That is, as age increases, the incidence of tumors increases. Certain families of both birds and mammals have, however, a much lower incidence than would be expected from the average age for the group. Other avian and mammalian groups have much higher percentages of tumor bearers than the average age seems to warrant. Mammals, generally, are more subject to new growths of the digestive organs and birds to new growths of the genito-urinary organs than to neoplasms affecting other parts of the bodies. The class Aves is, as a whole, less subject to tumor growth than Mammalia.

AUTHOR'S SUMMARY.

SYMPATHETIC TUMORS OF THE ADRENAL MEDULLA. E. SCOTT, M. G. OLIVER
and M. H. OLIVER, *Am. J. Cancer* **17**:396, 1933.

One hundred and fifty-eight cases of tumors with origin in one or both suprarenal medullas have been collected from the literature and classified on the basis of their structural differentiation. Four cases of sympathicoblastomas are reported from the authors' laboratories. A scheme for classification is adopted for sympathetic nerve tumors based on the present conceptions of the histogenesis of the cell types. The Pepper type of tumor of the suprarenal medulla may originate in the right, in the left or in both suprarenals; it frequently occurs congenitally; in the cases reviewed it occurred at an average age of 1.5 months when primary in both suprarenals, of 2.25 months when primary in the right and of 15.5 months when primary in the left; it was found in thirty cases from the literature and in one of the authors' cases; it is found only in the completely undifferentiated class of tumors. The Hutchison type of suprarenal tumor was found in thirty-eight cases from the literature; it may originate in either suprarenal, but was not found when the tumor was primary in both; it occurs at an

average age of 8.5 years when primary in the left suprarenal and at 3.5 years when primary in the right suprarenal. Both Pepper and Hutchinson types originating in the right suprarenal occur at earlier ages than do those arising in the left suprarenal. The younger the patient, the more undifferentiated are the tumor elements. The more undifferentiated the tumor, the greater are the number of metastases and the greater the degree of malignancy. Tumors with atypical metastases occur, as a rule, at older age levels and are more mature in structure. Sex does not appear to be a factor in the incidence of these tumors. The conclusions of Frew as to the relationship of the type of metastasis to the seat of the primary tumor do not seem to be borne out by a study of a larger number of cases. Any attempt at explanation of the underlying factors determining the type of metastasis is at present theoretical. Whether sympathicoblastomas, especially of the Pepper type, are truly metastatic, or whether the foci are heterotopic in origin has been discussed in the literature. According to Wiesel, rests of sympathetic building cells may occur on the undersurface of the liver in early fetal life. It is conceivable that as the liver grows, these cells may be carried into the hepatic tissue with the anastomosis of the vitelline veins and widely distributed with the blood vessels. Matzdorff, also, thinks that the tumors of the liver are not true metastases, but are primary from fetal rests. The distinctly earlier age at which the Pepper type appears might argue for the theory of a systemic origin of this type. However, in the records of all types of malignant sympathetic suprarenal tumors and in case 1 of our series, a probable congenital Pepper type, tumor cells were found filling the lymphatics and blood vessels of both the primary and the secondary growths. This fact is evidence for metastasis as one means of the distribution of the tumors.

AUTHORS' SUMMARY.

CULTURAL CHARACTERISTICS OF CYSTICERCUS CYSTS AND TWO CYSTICERCUS TUMORS. W. MENDELSON, *Am. J. Cancer* **17**:442, 1933.

The growth characteristics of the cells of IRS 146 and IRS 1548 were found to be essentially the same. The growth of IRS 146 and IRS 1548 was composed of malignant cells, connective tissue cells and mononuclear blood cells and macrophages. The characteristic malignant cell has a large, coarsely granular nucleus and a granular cytoplasm. It was found only in cultures of the tumor tissues. The cells which grew in cultures of fetal rat liver were the endothelial and mesothelial cells, the mononuclear blood cells and macrophages and a few hepatic epithelium cells. The growth of the wall of the 4 to 6 month old cyst in cultures consisted of the connective tissue cells, mesothelial cells, mononuclear blood cells and macrophages. The cells which migrated from the explants of the 15 day old vesicle were the endothelial and mesothelial cells, the mononuclear blood cells and macrophages and certain altered cells; these cells were derived for the most part from the rudimentary cyst wall. The supporting elements of the fifteen day infested liver manifest greater growth activity in cultures than those of the non-infested liver of a rat of the same age.

AUTHOR'S SUMMARY.

NEUROFIBROMATOSIS OF THE BLADDER. I. H. KASS, *Am. J. Dis. Child.* **44**: 1040, 1932.

A boy, 7 years of age, who had had a brown macular eruption of the skin and several subcutaneous nodules since birth, had hematuria of two days' duration. After injection of an opaque medium, roentgen study showed an asymmetric deformity of the bladder; an indurated growth was felt involving and lying between the rectum and the bladder. Death resulted from scarlet fever, bilateral otitis media and bronchopneumonia. The bladder was large, and its wall varied from 2 to 4 cm. in thickness. Numerous tumors projected from the surfaces and extended into the adjacent perivesicular tissue. The tumors of the bladder and the subcutaneous nodules were neurofibromas.

RALPH FULLER.

NEUROBLASTOMA OF THE ADRENAL WITH MULTIPLE METASTASES. JACOB KLEIN, *Am. J. M. Sc.* **184**:491, 1932.

A case of neuroblastoma (medulloblastoma) of the right suprarenal gland in a girl, aged 2½ years, is reported. The right suprarenal gland was completely replaced by an encapsulated tumor, which was soft in consistence and on section had a dark red, granular appearance. Microscopically, the tumor cells were arranged in groups (pseudorosettes), some of which showed necrosis in their centers. Glia fibers were demonstrated in the tumor by Hortega's method and by Mallory's glial stain. There was extensive visceral involvement (Pepper type) combined with numerous metastases in the lymph nodes, calvarium, humerus, ribs, orbital fat, liver, lungs and spleen.

SANDER COHEN.

IMMEDIATE CAUSES OF DEATH IN CANCER. SHIELDS WARREN, *Am. J. M. Sc.* **184**:610, 1932.

The immediate cause of death has been studied in 500 cases of carcinoma. Cachexia is the most frequent single cause, although exceeded by the total of the various pulmonary disorders. Cachexia is associated most frequently with cancer of the breast, stomach and large bowel. By far the commonest cause of death in carcinoma of the cervix uteri is renal insufficiency. Sepsis is an unimportant factor in fatal cases. The striking association of carcinoma of the buccal mucosa with pneumonia (36.2 per cent) and with abscess of the lung (56.3 per cent) emphasizes the rôle of aspiration in the production of these lesions.

AUTHOR'S SUMMARY.

MULTIPLE BENIGN CYSTIC EPITHELIOMA. F. SUMMERILL and J. G. HUTTON, *Arch. Dermat. & Syph.* **26**:854, 1932.

This comparatively infrequent tumor begins as a rule about the time of puberty or earlier, usually in female patients. It is symmetrical in distribution and usually appears on the face, but may occur on the neck, the chest, the upper parts of the arms and rarely on the lower limbs. It may affect two generations in succession, but rarely occurs in the third. It develops from the basal cells of the epidermis or hair follicles. It does not appear to change into basal cell carcinoma.

ACUTE LEUKEMIA FOLLOWING LYMPHOSARCOMA. KATSUJI KATO and ALEXANDER BRUNSCHWIG, *Arch. Int. Med.* **51**:77, 1933.

Two cases are reported in which the patients when first seen had lymphosarcoma with a normal blood picture; a short time later acute lymphatic leukemia developed, with a rapidly fatal termination. This is additional evidence in favor of the view that lymphosarcoma and lymphatic leukemia are different stages in the same pathologic process. Roentgen therapy was instituted in both cases immediately after the diagnosis of lymphosarcoma was made, and the question therefore arises as to whether or not this treatment induced the leukemic state.

AUTHORS' SUMMARY.

SQUAMOUS CELL CARCINOMA OF THE KIDNEY. J. RABINOVITCH, *Arch. Surg.* **24**:581, 1932.

A case of squamous cell carcinoma of the kidney is reported in which the tumor invaded the renal artery and produced complete infarction of the kidney.

N. ENZER.

ADAMANTINOMA. R. F. C. KEGEL, *Arch. Surg.* **25**:498, 1932.

Kegel reviews thirty-five cases. There seems to be a higher incidence of this tumor in the colored race. The majority of the tumors are located in the lower

jaw. The earliest age of incidence was 7 years; the oldest, 73; the majority of the cases occurred in persons of the ages between 11 and 35. The growth is slow and the duration long, and the tumor may reach a considerable size. Necrosis and fistulas occur. When the tumor involves the upper jaw, it usually extends into the antrum. Roentgen examination shows a central bone expansive tumor. The tumor may be polycystic or solid. The fundamental cell type is a basal epithelial cell with varying degrees of differentiation into enamel. The stroma may or may not be cellular. Keratinization, with epithelial pearls, alveolar formations and frequently papillary formations, is found. Mucoïd degeneration of the stroma is common.

N. ENZER.

ADAMANTINOMA: REVIEW OF REPORTED CASES. JOSEPH MCFARLAND and H. M. PATTERSON, *Dental Cosmos* **73**:656, 1931.

Adamantinomas arise in the jaws from the paradental epithelial debris and in the hypophysis from the squamous epithelial debris of the hypophyseal duct. Irritation may be a causative factor in these tumors in the jaws, but probably not in the pituitary gland. Adamantinomas, in whatever location, have approximately the same histologic structure. They are locally malignant but generally benign. They do not metastasize. (The two cases reported by Simmons seem to be exceptions.) They cannot be definitely diagnosed until exploratory operation and biopsy are performed. They usually occur in the upper and lower jaws and in the pituitary gland, but cases occurring elsewhere have been reported, two in the tibia, one in the upper lip and a doubtful one in the nasomalarpalpebral region. Adamantinomas of the jaws are more common than those of the pituitary gland. One hundred and sixty-six cases in the jaw have been reported. These occurred in women and men in the proportion of three to two; the average age of the patients at the time of entering the hospital was 40 years; the average duration of symptoms was seven years. They occurred in the lower and upper jaws in the proportion of five to one, and twice as often in the left side of the lower jaw as in the right side. In the upper jaw the two sides were evenly affected. There were about six cystic to one solid tumor. Only complete radical excision seems able to effect a cure. Twenty-six cases of adamantinoma of the pituitary gland have been reported, 90 per cent of which were suprasellar. The average age of the patients was 24 years, and the average duration of symptoms, three years. The two sexes were about equally affected. About 95 per cent of these tumors were cystic. Operation is always indicated but seldom curative, satisfactory results having been obtained in only three cases.

We were able to collect references to one hundred and ninety-six cases of adamantinoma in the medical and dental literature.

AUTHORS' SUMMARY.

STUDY OF THE CAUSATIVE AGENT OF A CHICKEN TUMOR. J. B. MURPHY and E. STURM, *J. Exper. Med.* **56**:705, 1932.

The inhibiting factor present in certain relatively slow-growing strains of chicken tumor I and in chicken tumor X is adsorbed from extracts of the desiccated tumors by aluminum hydroxide (Willstätter type C) and can be released in effective quantities from this combination by treatment with basic sodium phosphate.

AUTHORS' SUMMARY.-

EFFECT OF TESTICLE EXTRACT ON THE GROWTH OF CHICKEN TUMOR. I. E. STURM and F. DURAN-REYNALS, *J. Exper. Med.* **56**:711, 1932.

Extracts prepared from the testicular tissue of the rat, rabbit, fowl or bull, when injected together with extracts of chicken tumor I or with cells of this tumor, showed no definite effect of either enhancement or inhibition so far as concerned the resulting tumors.

AUTHORS' SUMMARY.

TUMOR-LIKE CONDITIONS IN RABBITS CAUSED BY FILTRABLE VIRUS. R. E. SHOPE, J. Exper. Med. **56**:793 and 803, 1932.

A tumor-like condition has been observed in a wild cottontail rabbit and has been found to be transmissible to both wild and domestic rabbits but not to guinea-pigs, white rats, white mice or chickens. The clinical picture of the experimentally produced condition and the pathologic picture of the original and of the experimentally produced tumors have been described. The tumor has the general appearance of a fibroma. The methods used in transmitting the condition and satisfactory routes of inoculation have been described and discussed.

The properties of the agent causing a tumor-like condition in rabbits have been tested experimentally and the conclusion reached that it is a filtrable virus. While the tumor-like condition and infectious myxoma differ markedly in their clinical and pathologic pictures, they have been found to be related immunologically. The relationships of the tumor-producing virus to the virus of infectious myxoma and of the tumor-like condition to malignant neoplasms have been discussed.

AUTHOR'S SUMMARIES.

SOME PHYSIOLOGICAL CHARACTERISTICS OF EPITHELIAL TUMORS OF THE MOUSE. L. SANTESSON, J. Exper. Med. **56**:893, 1932.

The histologic and physiologic characteristics of mouse tumor in vitro have been compared. Twenty-eight adenomas, thirty-one adenocarcinomas, eighteen carcinomas and a series of tumors from two transplantable carcinomas and from Ehrlich carcinoma were cultivated in vitro. The adenomas were characterized by cells of normal appearance, migrating quickly and organizing in thin membranes, a few mitoses, a large production of acid and a rapid digestion of fibrin and egg albumin. The carcinomas differed from adenomas in a less rapid and less extensive migration of epithelial cells, a tendency to grow in budlike formations, the presence of many mitoses, a lesser production of acid and a lesser digestion of fibrin and albumin. Ehrlich carcinoma differed from both adenomas and spontaneous carcinomas in the unhealthy state of the cells, their irregular growth and the occurrence of a great many mitoses. The production of acid was slight, and the digestion of egg albumin or fibrin less marked, and even entirely lacking.

AUTHOR'S SUMMARY.

CANCER SUSCEPTIBILITY IN RELATION TO COLOUR OF MICE. C. C. TWORT and J. M. TWORT, J. Hyg. **32**:557, 1932.

An examination of about 10,000 tumor-bearing mice appertaining to 240 experiments comprising 24,000 animals has been made to find whether there was any difference in sensitiveness of the skin to our carcinogenic agents according to the color of the coat and eyes. Self-colored animals (excluding pure white) were more sensitive to petroleum oils (weak agents) than the corresponding piebald ones; that is, a black was more sensitive than a black and white, etc. When tars (strong agents) were utilized instead of petroleum oils, an opposite state of affairs existed, the self-colored animal being more resistant than its piebald companion. This reversal may be explained on the grounds of cell tolerance. Pink-eyed animals (excluding pure white) had a greater all over sensitiveness of the skin to our agents than animals with pigmented eyes. On the whole, the most sensitive animal was the pink-eyed fawn. The frequency of hyaline degeneration of the spleen and marked thyroid enlargement was greater among pink-eyed animals, especially when fawn-colored, than among animals with pigmented eyes.

AUTHORS' SUMMARY.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

PAUL R. CANNON, *President, in the Chair*

Regular Monthly Meeting, March 13, 1933

HYPERTENSION COINCIDENT WITH RETROPERITONEAL GANGLIONEUROMA AND MULTIPLE AREAS OF SOFTENING IN THE BRAIN AND THE SPINAL CORD OF A YOUNG MAN. FLOYD H. JERGENSEN.

Hypertension (the blood pressure varying from 250 systolic and 120 diastolic to 274 systolic and 140 diastolic) was observed in a man 23 years of age. A ganglioneuroma, histologically moderately mature, was found in the retroperitoneal region, near the left kidney. The brain and spinal cord contained multiple foci of hemorrhagic softening. There was marked arteriosclerosis of the vessels of the brain, spinal cord and kidney, with moderate involvement of the arterioles of the heart and mild involvement of those of the lungs, liver suprarenal glands, pancreas, intestines and skeletal muscles. The left testis contained no mature spermatozoa. Although hypertension not otherwise explainable has been observed associated with paragangliomas which are embryologically related to the tumor in this case, it is believed that the high blood pressure in this patient can be explained best on the basis of generalized vascular and renal changes. The presence of the ganglioneuroma probably was only coincident.

HISTOPATHOLOGY OF TONSILS HARBORING STREPTOCOCCUS EPIDEMICUS IN PATIENTS WITH AND WITHOUT ARTHRITIS. I. PILOT.

In septic sore throat due to *Streptococcus epidemicus* a considerable number of patients become carriers of this organism. The tonsils as a rule remain enlarged and reddened, and exudate is present in the crypts. Some of the carriers have acute rheumatic polyarthritis indistinguishable from acute rheumatic fever. Others complain of persistent pains in the joints without signs of inflammation. Still others do not have arthritis or arthralgia but may have glomerulonephritis, endocarditis, erythema nodosum or related rheumatic manifestations.

Tonsillectomy was performed when the rheumatic symptoms became quiescent excepting in patients with arthralgia or persistent arthritis. These patients had symptoms in the joints which usually were relieved after the removal of the tonsils. The carrier state was terminated by excising the tonsils. Throat cultures for *Str. epidemicus* rapidly became negative. Cultures of the extirpated tonsils revealed these streptococci in predominant numbers and even in pure culture. Histologic examinations were made. All the tonsils showed chronic inflammation. The crypts often contained exudate cells, epithelium and bacteria. The lining epithelium at times was replaced by granulation tissues. Bacterial stains revealed cocci in crypts on the surface epithelium or deeper in the underlying lymphoid tissue which was infiltrated with polymorphonuclear or plasma cells. The cellular reaction in the tonsils of the patients with arthritis did not differ from that in the tonsils of those without arthritis. It is evident that the tonsil may be a focus of infection due to *Str. epidemicus*. In addition to the focus and the streptococci, an underlying hypersensitiveness of the articular tissues is

necessary for the development of articular symptoms. The improvement following the removal of the focus, terminating the carrier state for *Str. epidemicus*, indicated that these streptococci as well as other hemolytic streptococci are important factors in the etiology of rheumatic arthritis and arthralgia.

DISCUSSION

R. H. JAFFÉ: Nodules of granulation tissue are found around the capsule of the tonsil. The portals of entrance may also be the points of excretion of the organism.

MULTIPLE CARCINOID TUMORS OF THE ILEUM WITH REGIONAL METASTASES: REPORT OF TWO CASES. ELEANOR M. HUMPHREYS.

In two cases, occurring in white men, 60 and 66 years old, multiple carcinoid tumors were found in the ileum. In the first there were nine nodules from 6 mm. to 2 cm. in diameter, and in the second, two nodules measuring 5 mm. and 1.4 cm. The nodules had the gross and microscopic appearance of carcinoid tumors. Silver-reducing granules were demonstrated in the tumors in the first case, but staining with silver was not attempted in the second because of the long interval between death and autopsy. In both cases there were metastases in the regional mesenteric lymph nodes. The proof of relationship cannot be considered absolute in the second case because of the coexistence of other malignant tumors (in the lungs and the esophagus). However, the histologic evidence strongly favors the view that the growths in the mesenteric nodes were metastases from the intestinal tumors. In neither case were there any known symptoms referable to the primary or the secondary tumors, although the largest nodule in the first case had produced a definite narrowing of the lumen.

Carcinoid tumors of the small intestine, originally considered benign infiltrating neoplasms, are potentially or frankly malignant if the ability to form metastases is taken as a criterion. Including the two reported, at least thirty cases with regional or distant metastases are on record. Multiple tumors are more common than some of the reports indicate. With these two there are at least forty-one recorded cases, with nodules numbering from two to more than thirty.

In recent reports the relationship of these tumors to symptoms of acute or chronic intestinal obstruction has been emphasized. The manner in which stenosis and resulting symptoms are produced was well illustrated in the first case. Examination of a series of nodules of increasing sizes shows that two factors are concerned. The increase in size of the initial nodule, located chiefly in the submucosa, leads to the formation of a sessile or a slightly pedunculated polyp. The extension of tumor tissue into the outer coats is commonly accompanied by scarring and contraction of the serosa and muscularis. Thus narrowing results from a combination of reduction of the circumference of the intestine with the development of a polyp which still further reduces the lumen.

CARCINOID TUMOR OF THE RECTAL COLON. ALEXANDER BRUNSCHWIG.

A carcinoid tumor of the rectal colon, 5 mm. in diameter, occurred 8 cm. above the mucocutaneous junction of the anus. It was excised under local anesthesia. No symptoms had been referable to the growth. There seems to be no other report of carcinoid tumor in the rectal colon proved histologically by silver impregnation. A carcinoid tumor must be considered in the differential diagnosis of epithelial tumors of the rectal colon.

The complete report was published in *The Journal of the American Medical Association* (100:1171 [April 15] 1933).

VERRUCOUS AORTITIS WITH SPECIAL REGARD TO ANEURYSM FORMATION IN CHILDREN. B. H. NEIMAN.

In a series of 4,100 consecutive autopsies at the Cook County Hospital, verrucous aortitis was found 3 times. The first observation was in the body of an

11 year old white girl and the clinical diagnosis was rheumatic heart disease. In addition to the verrucous aortitis, there were rupture of the aorta above the valve, verrucous endocarditis of the mitral and aortic valves, and Aschoff nodules in the myocardium. The second observation was in the body of a 27 year old colored woman, in whom the condition was associated with acute myocarditis. In the third body, that of a 4 year old white girl, the verrucous aortitis was associated with an aneurysm which ruptured into the pericardial sac. The aorta had verrucae; the myocardium, inflammatory scars.

Histologic studies in all demonstrated productive endarteritis. In a circumscribed focus the infecting agent causes a fibrinoid swelling, the first reaction. Should this go on to a productive change, there is a proliferation of fibrocytes, round cells and large histiocytes. Necrosis then breaks the internal elastic membrane, the media and even the adventitia. Should the weakened wall be unable to support the force of the blood pressure, a rupture or an aneurysm results.

In the 11 year old girl, because of the Aschoff nodules in the myocardium, the aortitis was on the basis of rheumatic fever. In the 27 year old woman, acute myocarditis of nonspecific origin was found. In the 4 year old child, streptococci were demonstrated in the lesion and scars in the myocardium. This case was one of streptococcic aortitis with an end-result identical with that of rheumatic aortitis.

The vascular verrucae are similar to, if not identical with the endocardial verrucae. They are manifestations of endarteritis with productive, proliferative changes. Inflammatory changes of the aorta may result not only from the vasa vasorum, but also by way of the lumen. In the latter there is productive endarteritis.

Regular Monthly Meeting, April 10, 1933

FRANK MCJUNKIN, *Vice-President, in the Chair*

REGIONAL PATHOLOGY IN AMERICA. WILLIAM F. PETERSEN.

Presentations were made of maps indicating the geographic distribution of mortality in the United States for the following diseases: exophthalmic goiter, leukemia, pernicious anemia, diabetes, tuberculosis, poliomyelitis, syphilis, tabes, dementia paralytica, erysipelas, gastric ulcer and angina pectoris. The presentation involved a discussion of meteorological and other factors presumably involved in the distinct regional distribution of such diseases. In this the underlying physiologic mechanisms apparently operative are to be sought in periodic anoxemic stimulations.

A FATAL INFECTION BY CLOSTRIDIUM WELCHII IN A PATIENT WITH PULMONARY TUBERCULOSIS. H. C. SWEANY and ASYA STADNICHENKO.

Although Howard reported on nine patients with a terminal Welch bacillus infection arising in the gastro-intestinal tract, no record was found of an infection in a tuberculous patient. Sailer, Laws and Eiman described a patient in whom such a condition arose without preceding disease. The important feature was the development of a profound toxemia with an effect on the suprarenals resulting in a gradual lowering of the blood pressure.

In a similar case the process appeared to begin in the gastro-intestinal tract of a patient with a stationary type of advanced pulmonary tuberculosis. Beginning rather insidiously with hyperpyrexia, abdominal pain, collapse and lowered blood pressure, it ended in death within fourteen days. Necropsy twelve hours after death revealed the old tuberculous process in the right lung, moderate-sized tuberculous ulcers in the intestines and a gangrenous segment of the lower ileum, about 170 cm.

in length. There was no strangulation or thrombosis of the mesenteric artery. The liver extended to the third rib on the right and the third interspace on the left. On surfaces made by cutting, it was soft and slate gray. Other changes were relatively unimportant. There were numerous large gram-positive bacilli in the blood and all the organs. This micro-organism was an encapsulated anaerobe. It produced a "foamy" liver within eighteen hours in a rabbit killed ten minutes after intravenous inoculation. Cultural reactions (milk, agars, sugars, etc.) permitted classification of it as a presumptive type III Cl. welchii.

DISCUSSION

E. F. HIRSCH: Postmortem or agonal invasion of tissues by these bacteria may have occurred.

H. C. SWEANY: The clinical progress coincided with Cl welchii infection.

GENERALIZED LYMPH GLAND REACTION IN A TRANSITIONAL CELL CARCINOMA OF THE NARES. GEORGE MILLES and N. D. FABRICANT.

The response of the lymph glands of the body to stimuli depends on the nature and severity of the stimulus and the time during which it may act, as well as on the susceptibility of the various components of the lymph gland.

The following case illustrates these features:

A white man, 23 years of age, began to suffer from severe pain involving the right side of the head in April, 1931. This was followed shortly by progressive enlargement of the cervical glands, which in December, 1931, responded to radium. The enlargement recurred, however, and was resistant to roentgenotherapy.

He entered the Research Hospital in August, 1932, with severe pain limited to the right side and back of the head and pruritus of the right side of the nose and lips. His breathing was obstructed, his speech was garbled, and he was markedly emaciated. The skin was anemic, and a massive lobulated firm swelling occupied both sides of the neck. The right naris was completely obstructed and the left partially obstructed by large polypoid masses. The palate and pharynx bulged, and the mucous membranes were dry and thick. Enlarged lymph glands were noted in the armpits and groins, and the liver was large.

The blood had a moderate anemia, 1 per cent lymphocytes, 2 per cent large mononuclears and transitionals, 83 per cent neutrophilic polymorphonuclears and 14 per cent eosinophils. The urine contained blood, 4+ albumin and casts. The roentgenogram disclosed increased density over the right maxilla and nasal cavity, with involvement of bone. Lymph glands from the inguinal region showed a marked lymphoid and plasma cell proliferation with numerous eosinophil leukocytes. A cervical gland disclosed marked fibrosis with hyalinization, a dense infiltration with plasma cells and eosinophils and marked proliferation of the reticulum cells with the formation of large cells having one or two nuclei.

During the following month he was septic, and finally the respiratory obstruction became so marked that a tracheotomy was made. He died one week later.

At autopsy the palate was firm and infiltrated. The retropharyngeal mass was an abscess lined with lobulated friable tan tissue and communicating with a similar pocket in the left side of the neck. The glands here were enlarged to 3 cm., and in the center they were broken down. Similar firm enlarged glands were found in the mediastinal, abdominal, axillary and inguinal groups.

Microscopic sections of the nasal tissues revealed islets of anaplastic transitional epithelial cells surrounded by a dense plasma cell and eosinophilic infiltration. Metastases were present in many of the cervical glands. Some of them had the same reticulum cell and plasma cell proliferation found in the biopsy tissue. Similar changes were present in the abdominal and axillary glands.

A dissociable, pleomorphic streptococcus was isolated ante mortem from the blood stream as well as post mortem from the cervical lesions.

From the pathologic standpoint the difficulty of arriving at a definite diagnosis from the biopsy specimen received is apparent. However, the real difficulty came in the interpretation of the marked plasma cell response in association with an atypical or peculiar proliferation of reticulum cells and their apparent derivatives. From a study of the sections, transitions between mature lymphocytes, irritation forms and typical plasma cells can be readily traced. Similarly, transitions between the atypical large mononuclear forms and the occasional multinucleated cells, forms which in some instances are indistinguishable from Hodgkin's disease, from the reticulum cells can be seen.

Similarly the occurrence of a marked reticulum cell response may be associated with the development of a variety of atypical cells including giant cells, generally held specific for Hodgkin's disease.

Therefore, while Hodgkin's disease is an entity and its identification is based not only on its individual cell components—but more especially on their arrangement and numbers with relation to each other—not uncommonly the clinical features must be known to interpret correctly the changes found.

RECURRENT ECTOPIC PREGNANCY COINCIDENT WITH TUBERCULOUS SALPINGITIS. P. A. DELANEY.

A white married woman, aged 34, entered the hospital on Jan. 4, 1933, because of acute lower abdominal pain of twenty-four hours' duration that had become increasingly severe. She also complained of an accompanying sense of pressure against the bladder and rectum. On Dec. 9, 1932, she had experienced an initial attack of acute pain in the right upper quadrant, near the midline, that was controlled with morphine. About a week later she had slight menstrual "spotting" with backache and daily emesis; her last normal menstrual period had been late in November, 1932. Her past history was significant in that about eight years previously she had been operated on for a ruptured ectopic pregnancy of the right fallopian tube. She stated that she had never had any other pregnancy, nor had she ever had symptoms of tuberculosis.

The clinical diagnosis of left tubal pregnancy was confirmed at operation on Jan. 5, 1933, and a left salpingectomy was performed. Grossly the ostium of the oviduct was open, and the enlarged portion of the ampulla contained clotted blood and placental tissue but no embryo. The lower part of the ampulla and the isthmus were within normal dimensions; their mucosa or endosalpinx had prominent longitudinal folds and multiple small gray nodules. The serosa was everywhere smooth and without nodules. Microscopically, sections from the enlarged ampullary portion showed normal placenta while the rest of the ampulla and the isthmus had a hyperplastic glandular mucosa with ciliated bordering epithelium and multiple miliary tubercles. Solitary acid-alcohol-fast bacilli were found in different parts of the lower ampulla and isthmus. Unfortunately no pathologic report of the right tube removed eight years previously is available.

Tuberculous salpingitis complicating ectopic pregnancy is a relatively rare condition. In 1921, Greenberg, reviewing cases from the Johns Hopkins Hospital, reported that in 200 cases of tuberculous salpingitis there had been no associated ectopic pregnancy, and that none of 303 cases of ectopic pregnancy showed any tubal tuberculosis. In 1930, Behney, in his thorough study of 167 consecutive cases of ectopic pregnancy, reported a single case, while Urdan published a clinical study of 474 cases which failed to include any type of pelvic tuberculosis. Van Etten, in 1931 reported 1 case in 77 patients with tubal pregnancies operated on at Sloane Hospital, New York, from 1926 to 1930. A review of the literature for the past decade renders it apparent that the prevalent idea that tuberculous salpingitis is a frequent factor in the etiology of ectopic pregnancy is ill-founded.

AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

C. PHILLIP MILLER, *Secretary**Twentieth Annual Meeting, The University of Cincinnati, Cincinnati,**April 10, 11 and 12, 1933*PEYTON ROUS, *President, in the Chair*

A FILTRABLE VIRUS FROM A PANDEMIC DISEASE IN RABBITS. LOUISE PEARCE, PAUL D. ROSAHN (by invitation) and C. K. HU (by invitation), Rockefeller Institute for Medical Research.

In December, 1932, a highly contagious and fatal disease broke out with explosive force in our rabbit-breeding colony; it spread so rapidly that within a month every animal in the colony of 1,500 rabbits had been infected.

Clinically, the disease resembled smallpox in man, and we have given it the name of "rabbit-pox." It was characterized by fever, prostration, general adenopathy and a pocklike eruption of variable extent on the skin and mucous membranes. The incubation period was from five to ten days. In typical cases, the first sign of infection was the appearance of erythematous macules; in these areas papules then developed which later became umbilicated and covered with crusts. The lesions varied in size from minute points to nodules 1 cm. in diameter. They occurred singly, in groups or as confluent masses with extensive edema and, in some cases, with hemorrhage. The eruption occurred over the entire body but was most extensive on the ears, the eyelids and eyebrows, the lips, the nape of the neck, the trunk and the scrotum. The mouth, tongue, nose and pharynx were frequently involved, and a seromucous, purulent or clear blood-stained discharge from the nose was common. Ocular lesions were likewise of frequent occurrence, and in males the testicles usually showed nodular or diffuse orchitis with edema of the scrotum.

The degree and the course of the infection varied widely. In cases of severe infection the majority of the rabbits were markedly prostrated and were evidently extremely ill, but some animals with extensive lesions appeared to be in perfect health. Many animals showed an apparently complete recovery from a severe infection, the visible lesions healing with scar formation. Death frequently occurred within a few hours after the first signs of the infection were noted or after a period of days or weeks. The mortality varied with the breed, sex, age and physiologic status. Among animals under 2 weeks of age, the mortality approximated 100 per cent, but it decreased with age, until in normal adults it was less than 20 per cent. In the animals of Himalayan stock there were no deaths among adults, while in others, such as the Belgian rabbits, the death rate was extremely high. Abortions were frequent.

The acute phase of the pandemic lasted about four weeks. After this time, the daily incidence of fresh cases and of deaths dropped fairly abruptly. In general, the later cases were milder than the earlier ones, this being particularly noticeable in the young animals; however, instances of severe disease did occur.

The postmortem observations were variable and not always characteristic. The organs most consistently affected were the liver, the spleen and the lungs. In typical cases, the liver was enlarged, pale yellow and firm and showed numerous small, opaque, gray or pearly white nodules. The spleen was enlarged, dark red and firm and usually showed focal lesions comparable with those in the liver. The lungs as a rule showed similar small focal lesions and areas of consolidation or lobar pneumonia. Focal or diffuse lesions were found in many organs and tissues, including the suprarenal glands, ovaries, testicles, salivary glands, lymph nodes, bone marrow, subcutaneous tissue, fat, muscles and periosteum.

Histologically, the lesions showed a central area of necrosis surrounded by a zone of edema or hemorrhage and infiltration with mononuclear cells. Inclusion bodies were not found.

Experimental transmission of the disease was attempted early in the course of the pandemic. Since the results of bacteriologic examination and the clinical picture made it appear unlikely that we were dealing with any of the usual bacterial agents, the initial experiments were carried out with Berkefeld V filtrates of various organs and tissues injected intratesticularly. In other experiments, unfiltered suspensions were used. The organs employed included: testicles, liver, spleen, lungs, popliteal lymph nodes, brain, spinal cord, blood and skin. The results of the first experiments were successful in that orchitis and scrotal edema were pronounced within forty-eight hours, fever developed, the animals appeared ill and death occurred in from four to eight days. This condition has been produced successively from rabbit to rabbit by means of filtrates (usually testicular), and the agent is now in the fifteenth serial passage. Other routes of infection have also been successfully employed, namely, intracutaneous, subcutaneous, intravenous, intraperitoneal, intramuscular and intracerebral injection and nasal and conjunctival instillation.

It has been possible to reproduce all the clinical and pathologic features of the spontaneous disease, including recovery, by the use of small doses and certain routes of infection, in particular intravenous injection and nasal and conjunctival instillation.

The limits of dosage are high. Very small amounts are sufficient to produce pronounced lesions, and death has followed the intratesticular injection of 1 cc. of filtrate in a dilution of 1:8,000. Berkefeld N filtrates are also active. Unfiltered material, however, is much more potent than filtered material; 0.2 cc. of a dilution of 1:1,000,000 injected intradermally produces a definite lesion with swelling, edema, hemorrhage and necrosis. The agent is active in tissues stored in 50 per cent glycerin at icebox temperature for at least ninety-four days.

Recovery from either the spontaneous or the experimental disease is associated with a refractory state to reinoculation. Furthermore, the serum from animals that have recovered has the property of neutralizing the virus in a 1:1 serum-virus mixture, as shown by intracutaneous tests.

The identification of the virus is not yet complete. There is apparently no relationship with the agents of virus III disease of rabbits and of infectious myxoma as shown by cross-inoculation and by virucidal tests, and clinically and pathologically the conditions do not resemble each other. (The experiments with infectious myxoma were carried out by Dr. T. M. Rivers.) There is likewise no clinical resemblance to Shope's tumor. We understand from Dr. Carl Ten Broeck, who is making comparative experiments, that rabbits recovered from Shope's tumor and from this tumor plus infectious myxoma show an increased resistance to the rabbit-pox virus.

With respect to vaccine virus, there is apparently some relationship but not complete identity. Rabbits immunized with the New York City Board of Health vaccine virus were refractory to rabbit-pox filtrates variously applied, but intradermal injections of unfiltered pox virus resulted in a positive but highly modified cutaneous reaction. Adult rabbits immunized with vaccine virus do not contract rabbit-pox when exposed to "open" cases, but young immunized rabbits do. In these instances, the disease was considerably milder than that presented by normal control animals (litter mates). Furthermore, serum from animals immunized with vaccine virus has a definite, but only a partial, protective power against rabbit-pox virus. We have not been able to produce lesions typical of vaccinia in either the scarified cornea or the skin, but cytoplasmic inclusion bodies have been found in the corneal epithelium of early experimentally induced lesions. It should be noted that we have worked with only one strain of vaccine virus and have not yet employed the neurotropic strain.

Studies on the host range of the virus are in progress. We have not succeeded in infecting rats, but in one instance the virus was recovered from the testicle of a guinea-pig into which the material was injected intratesticularly. Mice have

been infected by the intracerebral route. With this procedure, death occurs in from four to six days, and the brain contains active virus. The virus is now in the fifth serial mouse-to-mouse passage. Animals of other species, including the calf, will be tested for susceptibility.

There have been reports of epidemics of generalized vaccinia attributed to neurovaccine. It is not certain whether this disease falls in this category, but the present indications are that it is not a generalized vaccinia as the term is ordinarily understood.

It should be mentioned that this was not the first time we had encountered the disease. Early in 1930 there occurred several examples of a comparatively mild infection in a small breeding colony shortly after the importation of some rabbits from Europe. We thought that we had been successful in eradicating the condition, and there were no recognizable cases until this last winter, approximately three years later. Whatever the source of the present pandemic may have been, it is obvious that the disease is a possible menace to a laboratory in which rabbits are employed and that, under certain circumstances, it may be an extremely serious one.

THE PATHOGENESIS OF TRICHINOUS MYOCARDITIS. GLEN L. DUNLAP (by invitation) and CARL V. WELLER, University of Michigan.

Although the histopathologic picture of trichinous myocarditis as seen in fatal human cases is well understood, there has been much uncertainty as to whether the characteristic inflammatory reaction is due to the presence of embryos in the wall of the heart or to toxic substances brought to the heart by the blood stream. Encysted forms are never found in the cardiac muscle. It has been shown experimentally that in white rats to which an adequate number of encysted embryos has been administered young embryos in active migration can be found in the interstitial tissue of the myocardium for a short period only, roughly from the eighth to the eleventh day after feeding. Coincidentally, a defensive inflammatory reaction is established. After the twelfth day, the invading organisms disappear from the myocardium and are never found encysted in fibers of the cardiac muscle.

FAMILIAL FACTORS IN ARTERIOSCLEROSIS IN RABBITS. PEARL M. ZEEK, University of Cincinnati.

The inbreeding of rabbits for about three years has resulted in the establishment of two strains (living under identical conditions); one is apparently free from arteriosclerosis, while in the other this lesion occurs spontaneously with an incidence of about 30 per cent.

THE CHEMICAL CONSTITUTION OF THE PROSTATIC CORPORA AMYLACEA AND PROSTATIC CALCULI. ROBERT A. MOORE and R. F. HANZAL (by invitation), Western Reserve University.

Microchemical and histochemical studies demonstrate that the prostatic corpora amylacea are composed fundamentally of nucleic acid and its hydrolytic products. Some of the nucleic acid is in combination with a protein, probably a protamine, and some is probably in combination with calcium. A small amount of lipoid, probably lecithin and sphingomyelin, is incorporated. It is possible that there is also some independent carbohydrate aside from that incorporated in the nucleic acid. Such a chemical composition is in harmony with the morphology of these structures. The larger calculi are composed essentially of the same constituents, plus an infiltration with crystalline and noncrystalline calcium phosphate and calcium carbonate.

FERTILITY IN THE MALE. DAVID L. BELDING, Evans Memorial of the Massachusetts Memorial Hospitals.

In order to evaluate fertility by examination of spermatozoa in human beings it is necessary to establish normal standards. The total number of spermatozoa per emission and the rate of production, as determined from a series of specimens, form

a good index of testicular activity. Some degree of correlation exists between a persistent low count and a low level of fertility. The viability of spermatozoa depends on the condition of the spermatozoa, the temperature at which they are held and the menstruum. Under favorable conditions spermatozoa have been kept alive for twenty-six days. Before spermatozoal morphology can be used as a basis for determining fertility, it is necessary to differentiate the immature and atypical forms which occur in fertile persons from the abnormal forms indicative of sterility.

AN EFFECT OF ANTERIOR PITUITARY HORMONE (PROLAN B) ON FLEXNER-JOBLING CARCINOMA OF RATS. O. M. GRUHZIT, Research Laboratories, Parke, Davis and Company, Detroit.

Considerable effort has been spent in the last few years in an endeavor to repress neoplastic growths by the use of various tissue extracts. Recent reports indicate the possibility of the inhibition of the growth of transplantable tumors in mice by the administration of potent extracts obtained from the urine of pregnancy. This extract, when given to immature or to nonpregnant female mice, hastens ovulation and luteinization as do the extracts of the anterior lobe of the pituitary gland. The extract is known as prolan B.

In a series of experiments, adult male rats were inoculated with Flexner-Jobling carcinoma and forty-eight hours after the inoculation were placed under treatment with from 250 to 500 rat units of prolan B daily for from twelve to fourteen days. Some of the control animals remained untreated; others were treated with phenolated water or with protein material obtained in the process of preparing the active hormone extracts. In addition, the anterior pituitary growth hormone was used for comparison. One hundred and twenty-four animals received prolan B and 110 control animals either remained untreated or received nonspecific treatment. Tumors developed in 87.5 per cent of the 124 animals treated with the hormone, and there was no effect in 12.5 per cent. Tumors developed in 88.9 per cent of the 62 untreated controls, and there was no effect in 11.1 per cent. Of the 48 animals treated with phenolated water, nonspecific protein and the anterior pituitary growth hormone, there was no effect in 13.8 per cent, and in 86.2 per cent tumors developed. The results suggest that the hormone obtained from the urine of pregnancy, when used in doses of from 250 to 500 rat units a day, caused no higher incidence of repression of tumor growth than occurred in the control group. The rate of growth of the tumors was the least in the animals treated with prolan B, in which it differed only slightly from that in the animals treated with phenolated water. The greatest rate of growth was noted in the control animals and in those treated with the growth hormone. It was similarly evident that the gain in weight was the least in the animals treated with huge doses of prolan B. The decreased rate of growth of the tumors in these animals was probably indirectly due to the same factors which interfered with their systemic well-being.

These experiments suggest that the retardation in the rate of growth of Flexner-Jobling carcinoma in rats was probably due to the nonspecific toxic effect of the extracts. The incidence of tumors in treated animals did not differ from that in untreated controls or in animals treated with nonspecific substances.

THE SEROLOGIC REACTIONS OF A NEW PROTEIN FROM MILK. L. S. PALMER and JULIAN H. LEWIS, University of Minnesota and University of Chicago.

The fat emulsion in cow's milk is stabilized by a layer of adsorbed material firmly held at the surface of the fat. If not the only, at least the most important substance acting as a stabilizer is a protein which can be isolated from cream after repeated dilution and reseparation by centrifugation. Although this process removes all soluble solids, the fat emulsion is as stable as in the original cream. When the emulsion is broken by churning and the butter fat removed by warming to 60 C. and pouring off, an aqueous solution remains which contains a protein that can be precipitated at a p_H of from 3.9 to 4. The general chemical composition of this protein, as well as the physical and chemical properties of its aqueous solution,

shows that is is not casein, lactalbumin or lactglobulin. Immunologic methods were used to differentiate it further from the other proteins of milk. The "membrane" protein acted as a good antigen, since guinea-pigs sensitized with it gave fatal anaphylactic reactions when the protein was injected intravenously. Slight reactions were obtained when animals sensitized with the membrane protein were given injections of casein and lactalbumin, but not when they were given the alcohol-soluble protein of milk. With lactglobulin, fatal reactions were obtained. Animals sensitized with the membrane protein and desensitized to casein, lactalbumin and lactglobulin reacted fatally to the homologous proteins. Identical results were obtained when sensitized uterine strip preparations were used. These experiments indicate that the membrane protein is distinct from the other milk proteins, but that it shows a relationship to them, probably based on species specificity, which is more pronounced with lactglobulin.

THE INFLUENCE OF THE LIVER ON THE DESTRUCTION OF BILE SALT. J. L. BOLLMAN and F. C. MANN, Mayo Clinic.

We have studied the excretion of bile salts in the urine of dogs following ligation of the common bile duct with extirpation of the gallbladder and following removal of the liver. We have modified the method of Gregory for the determination of bile salts so that it is adequate for the determination of fairly large amounts of the salts.

During the first day following ligation of the common bile duct and extirpation of the gallbladder, a very small amount of bile salts is excreted in the urine. The excretion then rises to about 500 mg. daily, and remains fairly constant for some time. The feeding of additional amounts of bile salts (1 or 2 Gm. daily) fails to increase the excretion materially. The intravenous injection of bile salts permits the recovery in the urine of approximately 50 per cent of the added salts. It appears that the dog with biliary obstruction is able to destroy or to fix considerable amounts of bile salts.

Following removal of the liver, the excretion of bile salts is not of sufficient magnitude to give a definite reaction with the Gregory method. Bile salts given intravenously, however, are almost completely recovered in the urine within twelve hours after administration. Destruction of bile salts does not occur in the absence of the liver.

CHEMICAL FINDINGS IN THE BLOOD AND URINE IN PATIENTS WITH SEVERE DAMAGE OF THE LIVER. STEPHEN MADDOCK, Boston City Hospital.

(No abstract furnished.)

EXPERIMENTAL HEPATIC INSUFFICIENCY PRODUCED BY MODIFIED ECK FISTULA AND ROENTGEN IRRADIATION. F. W. HARTMAN and V. SCHELLING, Henry Ford Hospital, Detroit.

The difficulty of producing marked hepatic insufficiency in dogs with high voltage roentgen irradiation alone led to the development of a modified Eck fistula, which may be performed in one stage and has a low mortality. The use of high voltage roentgen irradiation in combination with the Eck fistula produces readily controlled insufficiency with little cirrhosis. The functional studies demonstrate the difficulty of the bilirubin method when less than 3 mg. per kilogram is used, and show that the change in ratio between free cholesterol and cholesterol esters is a valuable diagnostic aid.

ATTEMPTED IMMUNIZATION OF RABBITS AGAINST EXPERIMENTAL SYPHILIS. G. E. WAKERLIN (introduced by A. J. CARLSON), University of Louisville.

In an attempt to produce artificial active immunity against experimental syphilis in rabbits, fourteen animals were each given a total of sixty-five injections, at four day intervals of 1 cc. of an extract (in physiologic solution of sodium chloride) of syphilitic rabbit testes, containing from five to six dead *Spirochetes pallidae* (Nichols strain) per dark field. In one half of the animals the preparation was

injected into the right testis, and in the other half it was given subcutaneously. Another group of eight rabbits was similarly treated with a control extract prepared from normal rabbit testes, one half of the animals of this group receiving injections intratesticularly and the other half subcutaneously.

The Wassermann reactions of all of the rabbits remained consistently negative during the two hundred and sixty day period.

Subsequent to the completion of the attempted immunization, in both groups of rabbits, as well as in a second control group of four untreated rabbits, the right testis was inoculated with the homologous strain of living *S. pallida*. Within the limits of individual variation, the incubation period of the active syphilitic infection, the severity and duration of the local lesions, the incidence and severity of the metastatic lesions and the duration of the positive Wassermann reaction were identical for each of the three groups.

The method of attempted immunization employed, therefore, was unsuccessful in the production of local testicular or generalized active immunity to experimental syphilis in the rabbit.

THE OCCURRENCE OF MONONUCLEAR PHAGOCYTES IN THE INFLAMMATORY EXUDATE IN LOBAR PNEUMONIA AND THEIR RELATION TO RESOLUTION. O. H. ROBERTSON, University of Chicago.

Certain striking histologic changes which we observed took place regularly in pneumonic lungs of dogs at the time of recovery from experimental pneumococcal pneumonia led to a study of the consolidated pulmonary tissue of human beings dying at different stages of lobar pneumonia.

We were fortunate to secure the lungs of a patient who died of nephritis six days following recovery from lobar pneumonia. The histologic picture of the lungs of this patient was very different from that observed in patients dying of the disease. The alveolar walls were markedly thickened, the alveoli were largely air-containing, and the cells of the exudate consisted chiefly of large mononuclears. The thickening of the alveolar walls was due to a general swelling of the septal cells, certain of which were partially detached from the walls and appeared to be entering the alveolar spaces.

A number of other cases showing varying stages of resolution were studied, and it was possible to follow this change from its beginning to the height of the reaction.

The earliest evidence of the production of mononuclear cells is the appearance of an occasional swollen lining cell of the septum. They also arise from the endothelium of the capillaries and probably from other structures of the supporting framework. As the reaction proceeds, more and more cells of the alveolar wall hypertrophy, become detached and gradually replace the polymorphonuclear leukocytes in the alveolar exudate.

These cells are actively phagocytic after they enter the alveolar spaces, and they appear to increase in size, many of the free cells being much larger than those in the alveolar walls. They appear to digest pneumococci rapidly, as many poorly stained forms are seen within them, and wherever resolution has progressed there are few or no pneumococci. The macrophages also engulf polymorphonuclear leukocytes and red blood cells.

Another possible function of the macrophages is that of the disposal of fibrin. When seen in the midst of a fibrin mass, they are usually surrounded by a clear zone, suggesting that the fibrin is being dissolved by enzymatic activity. Fragments of fibrin are also seen within the cells.

These observations in human beings, as well as those in dogs, suggest that the local development of large mononuclear phagocytes constitutes one of the important factors in bringing about resolution of the pneumonic exudate. Supporting this conception is the constant finding of this macrophagic reaction wherever resolution is occurring and its absence in consolidated areas which fail to show resolution.

OBSERVATIONS ON REPEATED ATTACKS OF EXPERIMENTAL PNEUMOCOCCIC LOBAR PNEUMONIA IN DOGS. L. T. COGGESHALL (by invitation) and O. H. ROBERTSON, University of Chicago.

Employing the method previously described for the production of experimental pneumococcic lobar pneumonia in the dog (*J. Clin. Investigation* 12:433 [March] 1933), we made a study of repeated attacks of the experimental disease. The constant relationship observed in our earlier work between the infecting dose and the outcome of the disease made it possible to determine with certainty whether a dog which had recovered from one attack was more or less susceptible to a subsequent infection. These observations include twenty dogs undergoing sixty-four infections produced at intervals of from three days to nine months.

It was found that the dogs which recovered from one attack of the disease survived subsequent infections induced by doses that regularly caused death in the initial attack. Furthermore, the secondary infections were mild and rarely involved more than a single lobe. Other evidences of the increased resistance of these dogs included: (1) the much reduced incidence and degree of bacteremia, (2) the occurrence of leukocytosis after infecting doses that regularly caused leukopenia in the primary attack and (3) the beginning development of the "macrophage reaction" in the pulmonary lesion within a few hours after its inception.

A study of the pneumococcidal activity of the blood serum showed that this property of the blood was irregularly present following the first attack or subsequent ones and had no apparent relationship to the dog's resistance to pneumococcic infection.

Tests were made on fifteen of the animals to determine whether or not hypersensitiveness to the pneumococcus developed as the result either of the primary attack or of the recurrent attacks of pneumonia. For this purpose a salt solution-pneumococcus autolysate was injected both subcutaneously and intrabronchially. No evidence of an allergic reaction was observed.

PROTECTION OF THE PERITONEUM AGAINST INFECTION. BERNHARD STERNBERG and HARRY GOLDBLATT, Toledo Hospital and Western Reserve University.

Heat-killed colic bacilli suspended in tragacanth were introduced into the peritoneal cavity of dogs. The mixture provoked an intense polymorphonuclear response of the peritoneum. Subsequent infections of the peritoneum, lethal in control dogs, were prevented, and the animals survived. The protection against infection and death is present within twelve hours after the introduction of the *Bacillus coli*-tragacanth mixture. The protection is due to phagocytosis of living bacteria by the polymorphonuclears already present in the peritoneal exudate. The phagocytosis is not specific since the polymorphonuclears evoked by the *B. coli*-tragacanth mixture ingest bacteria other than *B. coli*. This intense local polymorphonuclear response is due to the retention of the bacteria within the peritoneal cavity by the tragacanth.

THE EFFECTS OF LOCAL IMMUNIZATION ON THE DEVELOPMENT OF EXPERIMENTAL ABSCESES OF THE LUNG. W. MCC. TUTTLE (by invitation) and PAUL R. CANNON, University of Chicago.

Dogs were immunized against *Bacillus coli* and *Staphylococcus aureus* by spraying a vaccine prepared from formaldehyde-killed organisms into the main bronchi with a pressure spray apparatus introduced through a bronchoscope.

At intervals varying from fourteen to twenty-one days an embolus infected with homologous cultures of *B. coli* and *Staph. aureus* was introduced into the left external jugular vein. An embolus thus introduced lodges in the lungs and in normal animals gives rise to an abscess.

The animals were killed after varying periods up to thirty days, and the lesions were studied grossly and microscopically. Normal animals and animals immunized subcutaneously were used as controls.

The results indicate that lesions in the locally immunized animals are in general smaller and more sharply circumscribed than those in the controls. In some of the locally immunized dogs the embolus was surrounded by a dense wall of young fibroblasts and macrophages, within ten days, at which time well developed abscesses with irregular borders were present in the controls. Phagocytosis is prominent in the locally immunized animals, and repair is distinctly farther advanced than in the control after similar periods. Local immunization of the lungs, therefore, enhances the ability of the pulmonary tissues to overcome invading micro-organisms and to repair the local damage caused by them.

TISSUE EXTRACT AND BLOOD CLOTTING. H. P. SMITH, E. D. WARNER (by invitation) and K. M. BRINKHOUS (by invitation), State University of Iowa.

An extract of perfused pulmonary tissue in saline solution contains large amounts of thromboplastin or thrombokinase. This substance is instrumental in the conversion of prothrombin into thrombin. Pure pulmonary extract will not coagulate pure fibrinogen, even though calcium is present. We are, therefore, unable to accept the "tissue fibrinogen" theory of clotting as advocated by Mills. The clotting which does occur at times is slow and is due to contamination of the reagents with prothrombin or thrombin. Our experiments show that extremely minute traces of such impurities cause this slow type of clotting.

EXPERIMENTS ON THE CHEMOTROPISM OF LEUKOCYTES. MORTON McCUTCHEON and WILLIAM B. WARTMAN (by invitation), University of Pennsylvania.

Experiments were made to determine whether polymorphonuclear leukocytes are attracted by dead leukocytes. Human blood was centrifugated, and a small clump of leukocytes (from about 300 to 500 microns in diameter) was placed on a slide and allowed to dry. A drop of fresh blood from the same person was placed on the dead leukocytes and allowed to spread between the slide and the coverslip. The preparation was examined with the microscope at 37 C. The dead leukocytes were placed at one end of the microscopic field, and the number of leukocytes which moved to the dead ones and made contact with them was counted. Another field without dead leukocytes was then studied, and the number of leukocytes that made contact with an area of the same size as the clump of dead leukocytes was counted. In ten experiments, the number of moving leukocytes that made contact with the dead ones was eleven per hour; the number in the control fields making contact with the corresponding area was two per hour. It is therefore concluded that in these experiments polymorphonuclear leukocytes were attracted by dead cells.

SELECTION OF RETICULO-ENDOTHELIAL CELLS WITH THE MAGNET: METHOD AND FINDINGS. PEYTON ROUS and J. W. BEARD (by invitation), Rockefeller Institute for Medical Research.

Numerous functions are attributed to the phagocytic cells situated along the blood stream in certain organs, notably the liver, spleen and bone marrow. We have procured such cells from the liver by dislodging them with a stream of fluid after they have taken up an iron compound and sorting them out from the associated elements with a strong electromagnet. The cells thus procured exhibit characteristic features which they retain on cultivation.

THE FATE OF BLOOD PLATELETS. RAPHAEL ISAACS, Thomas Henry Simpson Memorial Institute for Medical Research, Ann Arbor, Mich.

From serum suspensions, stained by Wright's method, of cells of bone marrow, spleen and lymph nodes taken at biopsy, operation and autopsy, the tinctorial and morphologic changes in phagocytosed blood platelets have been studied. Platelets appear to be taken up in the spleen by large cells of the type that contain hemo-

siderin and other granules. They become less basophilic, and the aggregates of material become more compact and appear as groups of deep reddish-staining granules, with a faint element of blue. The granules finally disintegrate and become indistinguishable from the general structure of the cytoplasm of the phagocytic cells. In a spleen removed at operation from a patient with thrombopenic purpura, active decomposition of platelets in the cytoplasm of the phagocytic cells was noted, although the number in the peripheral blood was practically negligible. These platelets must have been from blood received by a transfusion or platelets produced by the patient himself but destroyed too rapidly.

THE DIFFERENCE IN THE CREATINE CONCENTRATION OF THE LEFT AND RIGHT VENTRICULAR MUSCLES OF THE HEART. DAVID P. SEECOF, CHARLES R. LINEGAR (by invitation) and VICTOR C. MYERS, Western Reserve University.

Embryologic, anatomic, pathologic and physiologic data were assembled which led to the idea that the muscles of the left and right ventricles were qualitatively different. Studies of the creatine concentration established chemical differences between the two ventricles.

The findings in the hearts of eighty-four patients from birth to 83 years of age examined within thirty-six hours post mortem and in nine fresh animal hearts obtained from the abattoir are presented. The concentration of creatine was found to be higher in the left ventricle than in the right. In human beings, the creatine content in the left ventricle ranged from 116 to 369 mg. per hundred cubic centimeters of blood and in the right ventricle, from 93 to 283 mg. In this series, the creatine concentration in the left ventricle averaged 211 mg., and in the right, 148 mg. The average absolute difference between the left and right ventricles was 63 mg., or 30 per cent. The series of animals showed creatine contents averaging 308 mg. per hundred cubic centimeters of blood for the left ventricle and 265 mg. for the right, an average absolute difference of 43 mg., or 14 per cent.

An analysis of the findings indicates that the variations in the creatine content of the left and right ventricles may be correlated with the age, the weight of the heart, the creatine content of the voluntary muscles and the retention of creatinine in renal disease.

The fact that the two ventricles have different creatine contents further supports the idea that separate consideration must be given to the left and right ventricles "in all attempts to unravel the exact mechanism of the ventricular pump."

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, April 13, 1933

V. H. MOON, *President, in the Chair*

CONGENITAL HEART DISEASE WITH PULMONARY ARTERITIS: INTERVENTRICULAR SEPTAL DEFECT, DEXTROPOSITION OF THE AORTA AND DILATATION OF THE PULMONARY ARTERY. HAROLD L. STEWART and BAXTER L. CRAWFORD.

The following case presented a rare combination of cardiac defects consisting of a solitary opening at the base of the interventricular septum, dextroposition of the aorta and dilatation of the pulmonary artery instead of the stenosis which is usually present in the tetralogy of Fallot. In association with these anomalies, there were well developed inflammatory and degenerative lesions in the pulmonary artery and in its branches. The patient, a previously healthy, noncyanotic white

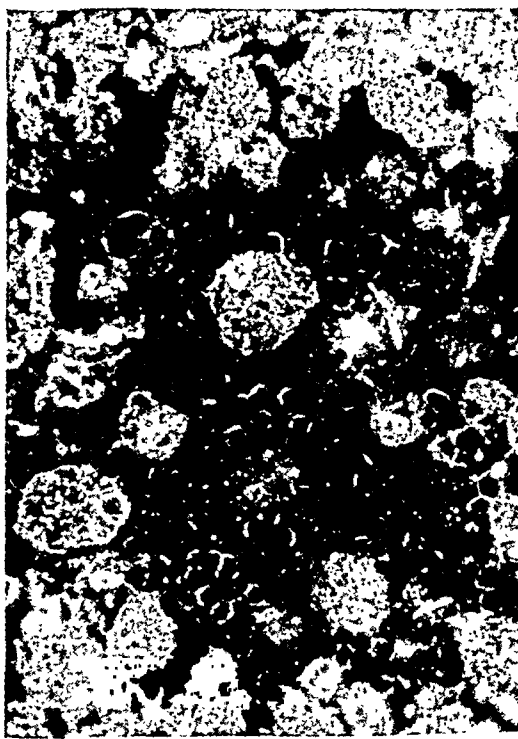
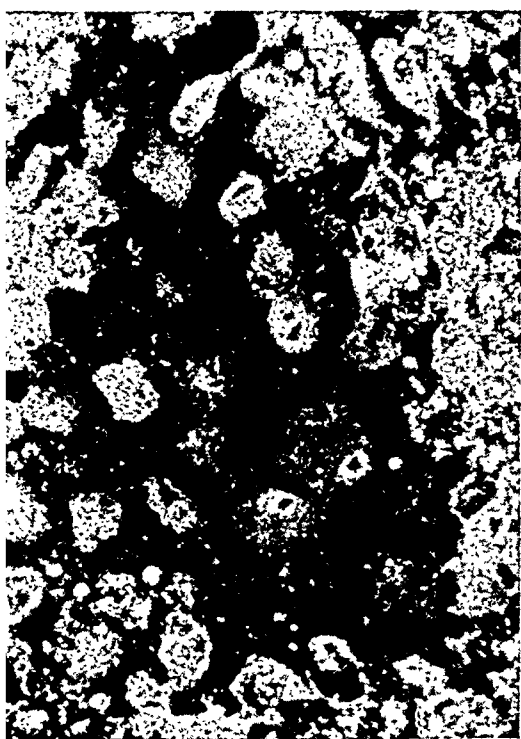
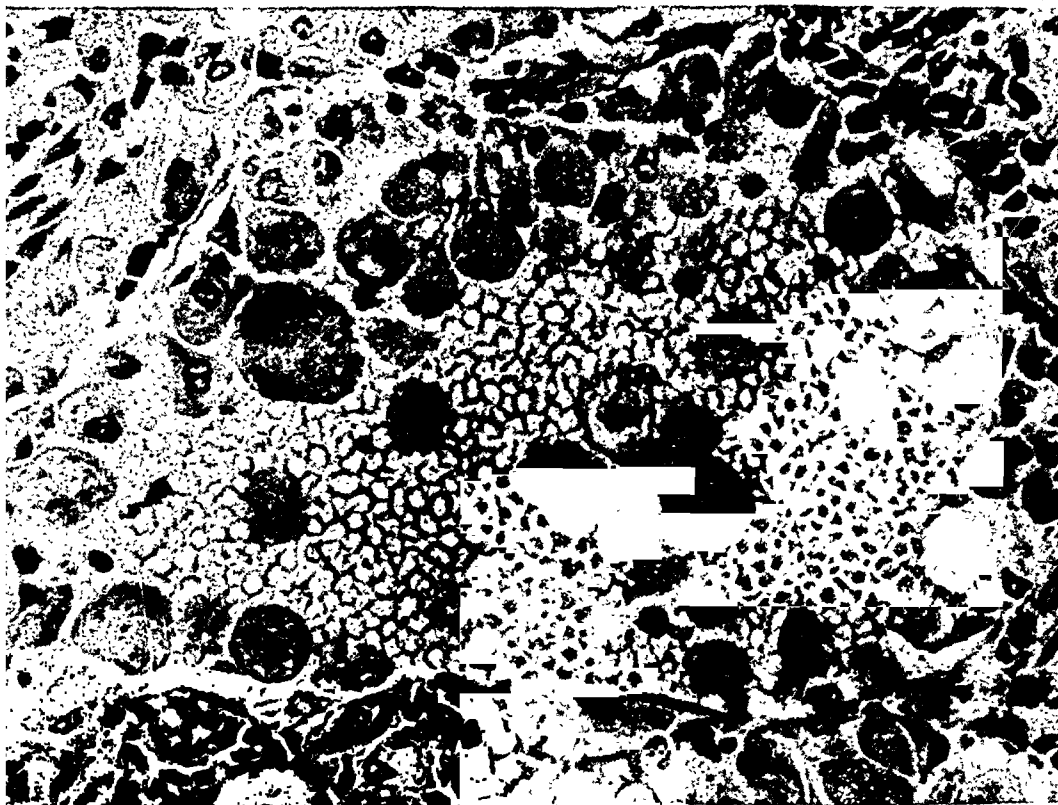
man, aged 60, a painter, gave no history of syphilis or rheumatic fever. Signs and symptoms of congestive heart failure developed, from which he died nine months after the onset.

The heart weighed 600 Gm. All the chambers except the right ventricle were dilated; the walls of both ventricles were markedly hypertrophied; the musculature contained numerous firm, grayish-yellow streaks and flecks. In the upper part of the ventricular septum there was a large funnel-shaped defect which measured 1 by 2.5 cm. and tapered from left to right, opening into the sinus of the right ventricle beneath the septal cusp of the tricuspid valve. The wall of the conus was hypertrophied. The lumen was somewhat narrowed as the result of compensatory hypertrophy of the crista supraventricularis which formed the anterior margin of the defect on the side of the right ventricle, screening the opening of the defect from the interior of the conus which opened into a dilated pulmonary artery. The pulmonary cusps were irregularly widened. The commissures were widened, and the free margins rolled inward. There were several massive aggregations of calcific material on the anterior and the right posterior pulmonary cusps. Above the cusps the pulmonary artery was dilated, inelastic, finely scarred and irregularly thickened by discrete and confluent atheromatous plaques. The aorta, which presented several patches of atheroma and calcification, was shifted to the right, overriding the ventricular septal defect so that it appeared to arise from both ventricles. The foramen ovale was closed, and the ductus arteriosus was obliterated. There were extensive thrombosis of the larger branches of the pulmonary artery and multiple infarction of the lung. Microscopically, the intima of the pulmonary artery and its branches was retracted by underlying scars and was irregularly destroyed and considerably thickened by atheromatous, calcific, fibrous and hyalinized plaques which penetrated deeply, replacing large portions of the media. The internal elastica was split, frayed and reduplicated, and in places it was much reduced. The intima contained a few small plaques consisting of necrotic cells with distorted and elongated nuclei, leukocytes and multinucleated cells. In the adventitia there were nodular and linear collections of lymphocytes, plasma cells and proliferating fibroblasts about the vasa vasorum, which were markedly thickened. The inflammatory tissue projected fanwise into the media, forming stellate scars which interrupted and replaced the muscularis and elastica. The smaller pulmonary arterial branches (3 mm. and less) were thickened, fibrosed and occasionally thrombosed; the internal elastica presented hypertrophy or atrophy, splitting, fraying and reduplication. The vessels were frequently surrounded by perivascular granulation tissue containing in some instances many lymphocytes, plasma cells and newly formed capillaries and at other times large amounts of connective tissue which sent stellate projections into the pulmonary parenchyma.

The patient died at the age of 60, which is almost double the highest age ever before attained by a patient with this combination of cardiac defects. As the anatomic conditions in the heart favored oxygenation, the admixture of venous with arterial blood was negligible, which accounts for the absence of clubbing of the fingers and until the last illness the absence of dyspnea and cyanosis. The relatively high pressure in the left ventricle, the healed pulmonary valvulitis, the contour of the ventricular septal defect and the patches of fibrosis on the endocardium bordering the defect and on the wall of the conus opposite support this assumption. The ventricular septal defect probably contributed to longevity by permitting the force of both ventricles to combine in propelling blood through the lesser circuit against the resistance offered by the sclerosed pulmonary arteries. With the onset of myocardial insufficiency, the shunt through the defect became venous arterial. The main branches of the pulmonary artery presented the characteristic lesions of degenerative atherosclerosis, which is rare with this combination of cardiac defects. In addition there was a well marked inflammatory lesion which had the characteristic appearance of those described as syphilitic, although the changes were not present in the aorta and there were no other lesions suggesting syphilis. The Wassermann reaction unfortunately was not determined. The lesion may possibly have been due to rheumatic fever, although it was not characteristic of that disease.

INCINERATION OF THE SPLEEN IN GAUCHER'S DISEASE. ESMOND R. LONG.

Recent extensive use of incineration in the study of various pathologic as well as normal tissues suggested its application as a supplement to other histologic methods in a case of Gaucher's disease that came under observation. The patient



Incineration of the spleen in Gaucher's disease.

was a 7 year old girl under the care of Dr. H. Epstein, who will report the case in detail later. The spleen was removed at the Jewish Hospital of Philadelphia. The diagnosis before operation was Gaucher's disease, and this was confirmed by microscopic study of sections and by chemical analysis. The latter, made by Dr. J. G. Reinhold at the Philadelphia General Hospital, disclosed the presence of 6.2 per cent kersasin, a finding now considered distinctive for Gaucher's disease, or cerebroside-cell hepatosplenomegaly, in the differential diagnoses of the lipoidoses (Epstein: *Virchow's Arch. f. path. Anat.* **281**:152, 1931).

The incineration study was made to determine whether a corresponding accumulation of inorganic material accompanies that of the cerebroside kersasin. The technic used was that of Policard (*Ann. d'anat. méd.-chir.* **1**:163, 1924; *Protoplasma* **7**:464, 1929) and Scott (*Compt. rend. Soc. de biol.* **190**:1073 and 1323, 1930; *Proc. Soc. Exper. Biol & Med.* **29**:349, 1932; *Am. J. Path.* **8**:329, 1932).

In general, the Gaucher cells were found to have a high content of ash in the nucleus and a low content in the cytoplasm as illustrated in the accompanying figure. Most investigators who have reported on incineration of tissues have called attention to the nuclear ash. In the study here reported the same peripheral distribution of ash was noted as described by Scott and Horning (*Am. J. Path.* **8**:329, 1932) in the nuclei of tumor cells and by Cowdry (*Am. J. Path.* **9**:149, 1933) in the nuclei of liver cells in yellow fever. The nucleoli conspicuous in the sections stained with hematoxylin and ecsin could also be observed in the ashed specimens, although not with regularity.

There was nothing distinctive in the distribution of the ash in the cytoplasm. Iron salts, which can be recognized by their color in ashed sections, were not observed. Degenerated cells, poor in material with staining affinity, were also poor in ash, and the large vacuoles characteristic of these cells in the usual preparations were seen in the corresponding incinerated cells.

The appearance of the erythrocytes (accompanying figure) was characteristic. The ash was concentrated at the peripheral border. Presumably this was an artefact caused by the fixation and drying of the specimen. However, the peripheral distribution of ash was as marked as that in the nuclei, and if one is an artefact of fixation, the question is properly raised whether the other is not also.

The total ash of a specimen from this case, incinerated in a crucible, was 2.7 per cent of the dry weight. This may be compared with the figure of 1.5 per cent of the moist weight, or approximately 6 per cent of the dry weight, commonly given for the normal spleen (Long: *Textbook of Physiological Chemistry*, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1909, p. 14). The incineration study furnishes the explanation for this decrease in ash per unit of weight. The ash is concentrated in the nuclei, and nuclei are present in much larger numbers per unit of volume or of weight in the normal spleen than in the spleen in Gaucher's disease, the bulk of which is largely due to the cytoplasm of Gaucher's cells, or cerebroside cells, which is relatively poor in mineral matter.

INFLUENCE OF RETICULO-ENDOTHELIAL "BLOCKADE" AND SPLENECTOMY ON EXPERIMENTAL TRYPANOSOMIASIS AND SYPHILIS AND THE CHEMOTHERAPEUTIC PROPERTIES OF ARSPHENAMINE AND NEOARSPHENAMINE. JOHN A. KOLMER and JAY F. SCHAMBERG.

1. Partial blockade of the cells of the reticulo-endothelial system of rats by intravenous injections of india ink slightly increased the resistance to infection with *Trypanosoma equiperdum*.

2. This partial blockade, however, had no demonstrable effects on the trypanocidal activity of arspenamine and neoarsphenamine.

3. Partial blockade in rabbits by intravenous injections of india ink had no appreciable effects on infection with *Spirochaeta pallida*.

4. The partial blockade likewise had no demonstrable effect on the spirocheticidal properties of arspenamine and neoarsphenamine.

5. Removal of the spleens of rats had no appreciable effects on the development and course of infection with *T. equiperdum* injected intraperitoneally from five to seven days later.

6. Splenectomy, however, definitely reduced the trypanocidal activity of both neoarsphenamine and arsphenamine administered from five to seven days later, since the minimal curative doses were almost twice as large as those used for control animals.

7. Removal of the spleens of rabbits had no appreciable influence on the development and course of acute testicular syphilis following inoculation with *S. pallida* approximately from three to four weeks after operation.

8. Splenectomy, however, definitely increased rather than decreased the spirocheticidal activity of arsphenamine.

9. While partial blockade of the reticulo-endothelial system with india ink has no appreciable effects on the trypanocidal and spirocheticidal activity of arsphenamine and neoarsphenamine, it is apparent that splenectomy profoundly influences the chemotherapeutic activity of these compounds.

THE PHILADELPHIA INSTITUTE FOR MEDICAL RESEARCH AND ITS RELATION TO
THE INTEREST OF PATHOLOGY IN PHILADELPHIA. L. G. ROWNTREE.

Dr. Rowntree outlined the purposes of the Philadelphia Institute for Medical Research and discussed investigations that are being undertaken by this group.

Book Reviews

Poliomyelitis. A survey made possible by a grant from the International Committee for the Study of Infantile Paralysis, organized by Jeremiah Milbank. Pp. 562, with 30 figures and 82 tables. Baltimore: Williams & Wilkins Company, 1932.

Dr. William H. Park, chairman of the International Committee for the Study of Infantile Paralysis, prefaces this volume with an acknowledgment of the contributions amounting to \$280,000 made by Mr. Jeremiah Milbank for the support of investigations on poliomyelitis since 1928, and with a brief account of the composition and program of the Committee. This book is one of the results of the Committee's activities.

The volume is a critical bibliographic survey of all the available published articles on poliomyelitis. Approximately 8,000 references were consulted, and many of the most important papers were abstracted in considerable detail. The arrangement of the material for orderly presentation was made by a group working under the leadership of Dr. Helen Harrington. The book contains seven chapters, the titles and authorship of which are as follows: I. "Historical Summary," by Elizabeth F. Hutchin; II. "Etiology," by Helen Harrington; III. "Resistance and Immunity," by Helen Harrington; IV. "Symptomatology," by Josephine B. Neal; V. "Treatment," by Josephine B. Neal; VI. "Pathology," by Helen Harrington; VII. "Epidemiology," by Mildred Weeks Wells. Each chapter was read by one or more members of the International Committee. A topical analysis of the chapters and a detailed index greatly aid the reader in gaining access to the large amount of information recorded in the book.

Although the material is presented in the form of a survey and review of writings on poliomyelitis, the author of each chapter has introduced paragraphs of critical comment at the beginning or end of each important subdivision. These may be regarded both as opinions of the authors and as a consensus of the members of the Committee. As these conclusions are not summarized in any special section, the reader discovers them only after perusal of the text.

It seems unnecessary to present an analytic review of this large volume, which is itself a review of the voluminous literature on poliomyelitis. A description of the plan and contents of the book is sufficient to indicate to those interested in this disease that a compact assemblage of a vast amount of information has been provided for their aid. The work was done with such care and thoroughness that no important papers have been overlooked. All points of view have been presented by the authors with fairness and in objective detail. In these days of multiplicity of scattered publication, this documented epitome of knowledge of all aspects of poliomyelitis is a most serviceable guide and reference book.

The illustrations are excellent and interesting. The graphs and tabulations are succinct presentations of valuable statistical and epidemiologic material. The press-work is evidence of the skill and care of the publisher.

Books Received

INTRACRANIAL TUMORS. Percival Bailey, Professor of Surgery, University of Chicago. Price, \$6.00. Pp. 475, with 155 figures. Springfield, Ill., Charles C. Thomas, Publisher, 1933.

PRACTICAL HEMATOLOGICAL DIAGNOSIS. O. H. Perry Pepper, M.D., Professor of Clinical Medicine, University of Pennsylvania; Assistant Chief of the Medical Clinic, Hospital of the University of Pennsylvania; and David L. Farley, M.D., Physician to the Pennsylvania Hospital, Philadelphia, and to the Cooper Hospital, Camden, N. J.; Associate in Medicine of the University of Pennsylvania. Price, \$6.00. Pp. 562, with 3 colored plates. Philadelphia: W. B. Saunders Company, 1933.

ARBEITEN AUS DEM PATHOLOGISCHEN INSTITUT DER UNIVERSITÄT HELSINGFORS (FINLAND). Begründet von weil. Prof. Dr. E. A. Homén. Herausgegeben von Prof. Dr. Axel Wallgren. Neue Folge. Sechster Band, Drittes und Viertes Heft. Mit 69 Abbildungen im Text. Jena: Gustav Fischer, 1931.

SURGICAL PATHOLOGY. William Boyd, M.D., M.R.C.P.Ed., F.R.C.P., London, Dipl. Psych., F.R.S.C., Professor of Pathology, University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Third edition. Pp. 866, with 477 illustrations and 13 colored plates. Price, cloth, \$10, net. Philadelphia: W. B. Saunders Company, 1933.

COLLECTED REPRINTS FROM THE LABORATORIES OF THE MOUNT SINAI HOSPITAL, NEW YORK, Louis Gross, M.D., Director, 1932.

ANATOMIC EVIDENCE OF FUNCTIONAL DISORDERS OF THE HEART

OTTO SAPHIR, M.D.

CHICAGO

The pathologist, at postmortem examination, is often confronted with the difficult task of deciding whether or not during life the heart has shown functional disorders, such as valvular insufficiency, stenosis of the valvular orifices or dilatation of the chambers. While the anatomic changes revealed at autopsy are often so pronounced that an abnormality of the physiologic activity of the heart can easily be deduced from the gross findings alone, there are many instances in which it is not possible from the gross or from the histologic changes to draw any definite conclusions as to physiologic disturbances. Between these two extremes, there are a number of cases which reveal certain anatomic changes which, after proper evaluation, may aid in the diagnosis of functional disorders. My purpose in this communication is to relate the results of a study of such intermediate cases and to correlate certain disturbances of the function of the heart which were diagnosed clinically with a number of grossly and histologically recognizable structural changes.

AORTIC INSUFFICIENCY

In a number of cases which were diagnosed clinically as aortic insufficiency, circumscribed whitish areas of endocardial thickening were found on the interventricular septum of the left ventricle. Often such thickenings were seen in the region of the trabeculae carneae where, in the form of fibrous cords, they sometimes bridged some of the trabeculae. More commonly, these thickenings were encountered in the endocardium of the lower third of the left ventricle. In more severe cases, they were found just beneath the aortic cusps. Occasionally, actual endocardial pockets could be found with their openings invariably directed toward the aortic valve. Among ninety-three cases of clinically recognized aortic insufficiency, such pockets were found in fifteen. In some instances, one or several rows of pockets resembling cusps of the aortic valve were found.

Aided by a grant from the Rosette Josephson Fund.

From the Department of Pathology of the Nelson Morris Institute of the Michael Reese Hospital and the Department of Pathology of the University of Illinois College of Medicine.

Histologically, the thickened endocardial areas may show either evidence of old inflammatory lesions or simple fibrosis and hyalinization. In a previous communication,¹ it was pointed out that according to the histologic changes these endocardial thickenings might be the result of either a mural endocarditis or a primary mechanical irritation. In the latter instance, it must be assumed that the regurgitating blood and pressure acting as a chronic irritant primarily produce circumscribed fibrosed areas of the endocardium. As soon as irregularities of the endocardium are formed, the continuous regurgitation with formation of eddies in these regions finally results in the formation of pockets.

These pockets have been the subject of much controversy. Zahn² considered them as characteristic of aortic insufficiency. Krasso³ spoke of diastolic pockets to indicate that they were the result of the columns of blood regurgitating during diastole. Ribbert,⁴ on the other hand, quoting Lotti, considered a possible congenital genesis for endocardial pockets. He mentioned several instances of circumscribed endocardial thickenings that were not associated with valvular defects, even though in some of his cases a valvular endocarditis existed. As was mentioned before, at autopsy it is often impossible to make a diagnosis of valvular insufficiency. The question naturally must be considered as to whether such findings as Ribbert described were the result of valvular insufficiency rather than a coincidental condition present since birth in hearts which showed evidence of valvular endocarditis even though valvular insufficiency, from examinations of the valves, was not apparent. Ribbert, however, considered an aortic insufficiency also of importance in the formation of these endocardial pockets.

In the present series, whenever endocardial pockets were found, clinical evidence of aortic insufficiency had been present. In several instances in which the clinical diagnosis of aortic insufficiency had not appeared on the patient's record, a check-up of the physical findings revealed the presence of a diastolic murmur over the aortic area and other clinical symptoms which could be interpreted to have been the result of aortic insufficiency. Endocardial pockets open toward the aortic valve were never encountered in normal hearts or in hearts which were the seat of congenital anomalies. From this material there is no reason for the belief that they are the result of a congenital anomaly. Diastolic endocardial pockets (Krasso), in my opinion, are absolute proof of aortic insufficiency.

Circumscribed endocardial thickenings alone, without the formation of endocardial pockets, may be indicative of a healed mural endocarditis

1. Saphir, O.: *Am. J. Path.* **6**:733, 1930.

2. Zahn, F. W.: *Verhandl. d. Kong. f. inn. Med.* **13**:351, 1895.

3. Krasso, H.: *Frankfurt. Ztschr. f. Path.* **37**:136, 1929.

4. Ribbert, H.: *Die Erkrankungen des Endokards*, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*. Berlin, Julius Springer, 1924, vol. 2, p. 184.

and therefore cannot be regarded as characteristic of valvular insufficiency. Only if by histologic examination primary inflammation can be ruled out as their cause may a mechanical genesis for their formation be accepted, but this will rarely be the case.

STENOSIS OF THE AORTIC ORIFICE

The recognition of this condition at autopsy is probably easier than that of aortic insufficiency, because of the fact that it is usually caused

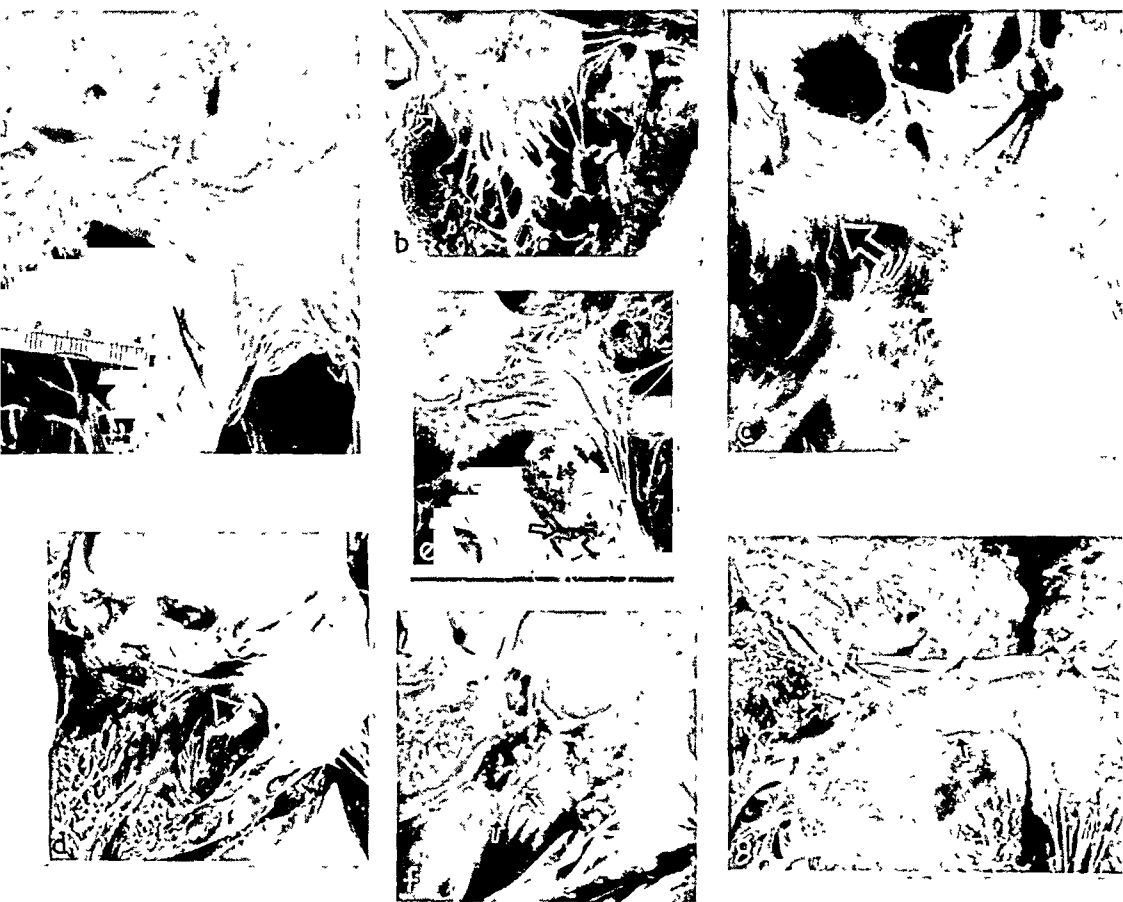


Fig. 1.—Anatomic studies showing: *a*, endocardial thickenings beneath the aortic valve with minute diastolic pockets (syphilitic aortic insufficiency); *b*, circumscribed endocardial thickening (stenosis of the aortic orifice); *c-c*, diastolic pockets (healed endocarditis of the aortic valve, with insufficiency); *f*, diastolic pockets (subacute bacterial endocarditis with insufficiency of the aortic valve), and *g*, systolic and diastolic pockets (syphilitic aortitis with insufficiency of the aortic valve, marked hypertrophy and dilatation of the heart, and relative stenosis of the conus aorticus).

by adhesions between the lateral parts of the cusps. Such adhesions, even though they may be slight, are easily recognizable. In several of the cases in the present series, circumscribed areas of endocardial

thickenings were noted just beneath the aortic valve. Occasionally, such regions revealed small openings which were directed toward the apex of the heart. Histologically, these lesions are similar to those seen in cases of aortic insufficiency. Pockets open toward the apex are encountered less frequently than those open toward the aortic valve. In this series, they were found in four of fifty-one cases of stenosis of the aortic orifice. Krasso named the pockets with their opening directed toward the apex of the heart, "systolic pockets," and claimed that they were significant of stenosis of the aortic orifice.

In the present study, systolic pockets were more commonly encountered in hypertrophic and dilated hearts, revealing a relative stenosis of the conus aorticus,⁵ than in cases of stenosis of the orifice of the aortic valve. When present, they were found just beneath the narrowed conus. In five cases of this series, these pockets led to the discovery of the stenosis. It might be of interest to mention that in four instances the stenosed conus and systolic pockets were found in cases of syphilitic involvement of the aortic valve with insufficiency of this valve and with typical diastolic pockets. The hypertrophy and dilatation of these hearts, due to aortic regurgitation, had led to the relative stenosis of the conus arteriosus. It was pointed out previously that it is possible that the friction of the systolic blood stream and pressure are sufficient to produce the mechanical irritation of an area situated in the region of the stenosed conus. At the same time, the continuous impulse of the systolic blood stream and pressure might result in the formation of pockets.

Systolic pockets have often been recognized and their significance disputed. Kaewel⁶ reported systolic pockets in one case without apparent stenosis of the aortic orifices. Böger⁷ denied the presence of valvular disease in one of his cases. In both instances, however, a relative stenosis of the conus aorticus could not be ruled out. Wertkin⁸ recently held the systolic blood stream responsible for the formation of systolic pockets in cases of relative or absolute stenosis of the aortic conus. Wolff⁹ believed that both the primary circumscribed endocardial thickening and the secondarily formed systolic pocket were the results of the systolic pressure in his case of stenosis of the aortic orifice. Krasso, however, maintained that the primary endocardial thickening which later may be the seat of a systolic pocket is the result of the

5. The conus aorticus, often called conus arteriosus sinister, is the uppermost portion of the left ventricular cavity, just below the aortic valve (Krasso).

6. Kaewel, H.: *Beitr. z. path. Anat. u. z. allg. Path.* **79**:431, 1928.

7. Böger, A.: *Beitr. z. path. Anat. u. z. allg. Path.* **81**:441, 1929.

8. Wertkin, I. M.: *Virchows Arch. f. path. Anat.* **280**:87, 1931.

9. Wolff, K.: *Virchows Arch. f. path. Anat.* **280**:107, 1931.

regurgitating columns of blood in cases in which there is also an aortic insufficiency. If, in addition to the valvular insufficiency, a stenosis of the aortic conus exists, systolic pockets may be formed secondarily. In other words, systolic endocardial pockets, according to Krasso, signify both stenosis of the aortic conus and insufficiency of the aortic valve. Because of the fact that in a number of my cases and in instances reported in the literature systolic pockets were present without

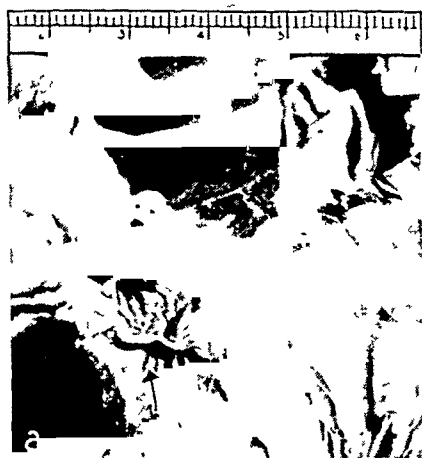


Fig. 2.—Anatomic studies showing: *a*, systolic pockets, stenosed conus aorticus and perforated septum (probe); *b*, right ventricular aspect of heart shown in *a* (note the perforated septum (probe), thickened medial leaflet of the tricuspid valve and pocket); *c*, perforated fossa ovalis and auricular pocket, the opening of which is directed toward the perforated fossa ovalis; *d*, defect in membranous septum, and *e*, right ventricular aspect of heart shown in *d* (note the septum defect, the thickened medial leaflet of the tricuspid valve and the huge vegetation to the right).

any evidence of aortic insufficiency, it must be emphasized that systolic pockets are pathognomonic of stenosis, either of the aortic orifice or of the conus aorticus.

INSUFFICIENCY OF THE MITRAL VALVE

In the course of this study, circumscribed areas of thickenings in the left auricle were encountered in four instances of healed endocarditis of the mitral valve. In two other cases, endocardial pockets, their openings directed toward the mitral valve, were present in the left auricle. One of these cases was reported elsewhere. In all these instances an underlying primary inflammation could be demonstrated histologically, with the presence of many lymphocytes, endothelial cells and a few polymorphonuclear leukocytes, in addition to much fibrosis. While these findings easily explain the circumscribed areas of thickenings on the basis of a primary inflammation, they fail to explain the formation of pockets. It must be assumed that another causative agent transformed these circumscribed areas of thickening into pockets. Because of the fact that these pockets were open toward the mitral valve, it is likely that whatever had caused their formation must have come from the direction of the mitral valve. The only possible explanation of a force exerting its effect from this direction is that of a regurgitating blood stream and pressure due to insufficiency of the mitral valve. In other words, endocardial pockets in the left auricle with openings directed toward the mitral valve are pathognomonic of insufficiency of the mitral valve.

PHYSIOLOGIC PATENCY OF A SEPTUM DEFECT, FORAMEN OVALE
AND PERFORATED FOSSA OVALIS

In the present series two cases were encountered which revealed morphologic evidence of the flow of blood through a patency in the intraventricular septum. The first case revealed an old endocarditis of the aortic valve and a marked hypertrophy and dilatation of the heart. The conus aorticus was narrowed. Within a distance of about 1.5 cm. from the base of the aortic valve, a series of three endocardial pockets was found, their openings directed toward the apex of the heart (systolic pockets). The endocardium between the base of the aortic valve and the endocardial pockets showed many areas of endocardial thickening and a perforation which led from the left into the right ventricle. The diameter of the perforated area in its left ventricular aspect measured 8 mm. and in its right 5 mm. The medial tricuspid leaflet corresponding to the perforation was thickened and showed a hematoma. Just beneath the perforation in the right ventricle there was an endocardial pocket, the opening of which was directed toward the perforation. In the periphery of the pocket several small areas of endocardial thickening could be made out.

The presence of the endocardial pocket in the right ventricle corresponding to the perforated septum is significant. No sections were

taken from this pocket, and therefore it cannot be decided whether or not the primary endocardial thickening which preceded the formation of the pocket in the right ventricle was the result of a healed mural endocarditis. It is equally possible that the force of the blood stream and pressure coming through the perforated septum might have caused the thickening merely by mechanical irritation. The continuous pressure directed on the fibrosed region secondarily had caused the formation of the pocket. The best explanation which can be offered for these pockets, therefore, lies in the assumption that during life, blood must have circulated through the perforated septum. In other words, this pocket is an anatomic witness of the interchange of blood between the ventricles. The presence of the systolic endocardial pockets in the left ventricle may be taken as proof of stenosis either of the aortic orifice or of the conus aorticus. The perforation of the septum was probably the result of an old ulcerating mural endocarditis.

Sternberg¹⁰ described one case which in many respects was similar to this one. He did not believe that the systolic pockets in the left ventricle were the result of a congenital anomaly, but stressed a mechanical genesis. He also emphasized that a mural endocarditis might accentuate the primary endocardial thickening which led to the formation of pockets.

The other case in this series was that of a child about 1 year old. At autopsy, the heart revealed a patent membranous septum. The margin of the opening at its right ventricular aspect was thickened and white. The medial leaflet of the tricuspid valve corresponding to the region of the defect in the septum revealed a circumscribed area of thickening. At the thickened portion of the medial tricuspid leaflet a large gray, soft, and friable vegetation was found, which on smears revealed many gram-positive cocci. The remainder of the tricuspid was tender, smooth, and glistening. There also was an organizing bronchopneumonia. The blood culture, taken at the time of autopsy, revealed hemolytic streptococci.

The circumscribed thickening of the tricuspid leaflet was the result of the mechanical irritation brought about by the columns of blood and pressure of the blood which circulated through the hole in the septum. When bronchopneumonia developed, and as a result of the bronchopneumonia a bacteremia, the bacteria selected the site of the primary injury of the tricuspid and caused the endocarditis. In other words, both the thickened portion of the tricuspid and the final acute vegetative (bacterial) endocarditis of the tricuspid make it evident that during life blood must have circulated through the patent membranous septum. It may be of interest to mention that Sternberg also described three cases

10. Sternberg, C.: *Verhandl. d. deutsch. path. Gesellsch.* **25**:238, 1930.

of defect in the septum with circumscribed thickenings of the sub-valvular region of the right ventricle. Two of his cases also revealed circumscribed thickenings of the tricuspid valve corresponding to the patency in the septum.

The next two instances reveal evidence of circulation of blood through a perforated fossa ovalis and a patent foramen ovale, respectively. The first heart revealed an acute verrucous and ulcerating endocarditis of the mitral valve, superimposed on a healed endocarditis. In the region of the fossa ovalis there was a round opening measuring about 8 mm. in diameter, the wall of which was thickened, firm and slightly ragged. This opening had established a communication between the left and the right auricles. Between this opening and the posterior leaflet of the mitral valve there was one large somewhat horse-shoe-shaped pocket with two smaller ones, the openings of all of which were directed toward the perforated fossa ovalis. Because of the size and form of the perforation and because of the presence of inflammatory cells, it is more likely that the perforation was the result of a mural ulcerating endocarditis in the region of the fossa ovalis than a primary patent foramen ovale.

The auricular pockets are significant because they point toward a flow of blood through the perforated fossa ovalis. The sections of the pockets revealed simple fibrosis and hyalinization but hardly any inflammatory cells or blood pigment. Therefore, it is likely that the pockets were caused by simple mechanical irritation brought about by the columns of blood and pressure of the blood circulating through the perforated fossa ovalis. This irritation first produced circumscribed endocardial thickenings and secondarily the pockets. The pockets also indicate that blood must have circulated from the right into the left auricle.

The second case of this group revealed an old and a recent verrucous endocarditis of the mitral valve. The myocardium showed many Aschoff nodules. There was a patent foramen ovale. The free margin of the foramen in one aspect was studded with small gray verrucae similar to those on the mitral valve. They were found only on the right auricular surface of the free margin of the foramen ovale. It might be emphasized especially that verrucae were present in these two locations only. The acute verrucous endocarditis of the free margin of the foramen ovale is significant from several points of view. First, the presence of verrucae confined to the free margin of the foramen ovale may be taken as evidence that the foramen ovale was patent during life and that blood passed through it. Second, the conclusion may be drawn that blood circulated from the right into the left auricle because of the fact that only the right auricular portion of the foramen ovale showed the verrucae. This corresponds to the finding of verrucae at

the line of closure at the auricular aspect of the mitral valve. Third, these findings may indicate that whatever had caused the appearance of the verrucae was brought to the margin of the foramen ovale through the circulating blood rather than through endocardial vessels, because otherwise their presence confined to this particular location cannot be explained. If this is true, it is much more likely that a verrucous valvular endocarditis also is the result of an injury brought to the valve by the



Fig. 3.—Anatomic study showing the verrucae at the margin of the foramen ovale.

passing circulating blood rather than by means of intravalvular blood vessels. As far as the scope of this paper is concerned, it must be emphasized that a verrucous endocarditis of the free margin of the foramen ovale is evidence of blood circulating from the right to the left auricle.

DILATATION OF THE HEART

This diagnosis can often be made from the gross observation of flattened papillary muscles and trabeculae carneae or of flattening of the inner walls of the cardiac chambers. According to statements in

the literature (Dehio,¹¹ Mönckeberg¹²), hyperplasia of the interstitial connective tissue of the heart (myofibrosis cordis) is characteristic of dilatation of the heart. Hyperplasia of the interstitial connective tissue was a common finding in the dilated hearts used for this study. Sometimes, however, difficulties arose in distinguishing myofibrosis cordis from connective tissue proliferation from other causes.

In a previous study in collaboration with Karsner,¹³ it was noted that segmentation of the muscle fibers was especially frequently encountered in hypertrophic hearts. It was observed at that time that the intercalated disks became distinctly visible in dilated hearts. The conspicuous appearance of the intercalated disks was called "readiness toward separation of the heart muscle fibers." In this study, therefore, special attention was directed toward the appearance of the intercalated disks. While in the nondilated hearts the intercalated disks were hardly noticeable, by the use of the hematoxylin-eosin stain they were prominent and easily demonstrable in the dilated hearts. They were more pronounced in the muscle fibers situated close to the endocardium than in those close to the epicardium. Since particular attention has been paid to the intercalated disks, it is possible to confirm a histologic diagnosis of dilatation of the heart by the autopsy records of flattened papillary muscles and columnae carnaeae. Whether the prominence of the intercalated disks alone offers sufficient ground to warrant a diagnosis of dilatation of the heart is at present difficult to decide, since so little is known of the purpose and function of the disks. However, from this study it appears that the conspicuous appearance of the intercalated disks in a large number of hearts is often characteristic of dilatation of the chambers.

SUMMARY

Endocardial pockets of the left ventricle which are open toward the aortic valve are pathognomonic of insufficiency of the aortic valve. Endocardial pockets in the left ventricle which are open toward the apex of the heart are pathognomonic of stenosis either of the orifice of the aortic valve or of the conus aorticus. Pockets in the left auricle with their openings directed toward the mitral valve are characteristic of insufficiency of this valve. Left auricular or right ventricular pockets with their openings directed toward a perforated auricular or ventricular septum, respectively, are indicative of an *intra vitam* circulation of blood through the perforated region in the direction of the openings

11. Dehio, K.: Deutsches Arch. f. klin. Med. **62**:1, 1898.

12. Mönckeberg, J. G.: Die Erkrankungen des Myokards und des spezifischen Muskelsystems, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 290.

13. Saphir, O., and Karsner, H. T.: J. M. Research **44**:539, 1924.

of the pockets. A circumscribed endocarditis of the tricuspid valve in an area corresponding to a defect in the interventricular septum indicates a flow of blood from the left to the right ventricle through the patency in the septum. A recent verrucous endocarditis at the right auricular aspect of the margin of a foramen ovale signifies a flow of blood through the foramen from the right to the left auricle. Two cases illustrating these conditions are reported. Prominent intercalated disks favor the diagnosis of a dilatation of the heart.

LYCOPodium GRANULOMA

ITS CLINICAL AND PATHOLOGIC SIGNIFICANCE, TOGETHER WITH A
NOTE ON GRANULOMA PRODUCED BY TALC

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The inflammatory reactions produced experimentally by means of the spores of *Lycopodium* have been extensively studied for many years and are well known. That these spores may be of importance in the production of lesions in man simulating tuberculous or neoplastic disease is not generally appreciated and needs to be emphasized. The problem was brought to my attention by a series of puzzling cases in which persistent sinuses, masses or tubercle-like lesions developed at the sites of previous operations. The nature of these lesions was at first not clear. However, microscopic examination of the surgical specimens revealed the common etiologic factor to be the spores of *Lycopodium*. Investigations showed that *Lycopodium* had probably been introduced into the wounds at the time of previous operations in a dusting powder of which it is an ingredient. Inquiry established the fact that powders containing spores of *Lycopodium* are used in the operating rooms of hospitals in the preparation of gloves and other rubber supplies.

REPORTS OF CASES

CASE 1.—A Spaniard, aged 35, was admitted to the hospital because of a persistent sinus and a mass in the epididymis. A history was obtained of an operation for traumatic hydrocele two months previously. A clinical diagnosis of tuberculous epididymitis was made, and an orchidectomy was performed. In the surgical specimen, the epididymis was found to be replaced by a firm, pearly white tissue, in the meshes of which were cellular and necrotic areas. Microscopic examination revealed the cellular areas to be composed of a type of granulation tissue containing numerous plasma cells, lymphocytes and giant cells of both the foreign body and the Langhans variety (fig. 1 *A*). Polymorphonuclear leukocytes were abundant in the more superficial layers. Within the granulation tissue, as well as within the giant cells proper (fig. 1 *B*), spores of *Lycopodium* as described later were found.

CASE 2.—During the course of a nephrectomy for pyelonephritis, in an 8 year old boy, a persistent renal sinus tract was encountered and resected. The history revealed that the condition had developed two months after the drainage and subsequent removal of a perinephric hematoma. Examination of the sinus tract showed a histologic picture similar to that in case 1. Spores of *Lycopodium* were also found within the sinus tract.

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Presented at the New York Pathological Society, Oct. 8, 1931.

CASE 3.—A man, aged 54, gave a history of the removal of stones from the urinary bladder eight years previously, with periodic irrigations since that time. Another stone had been removed from the bladder six weeks previously. On admission to the hospital, a fleshy polypoid bar of prostatic tissue causing obstruction at the vesical neck was seen by cystoscopy. This was diagnosed as a carcinoma, and three small specimens were removed by means of a prostatic punch. On microscopic examination, the tissue was seen to contain areas of round cells and of plasma cells interspersed with nodules the size of a millet seed composed of epithelioid cells, giant cells and vacuolated cells, the latter being probably of histiocytic origin. Occasional small necrotic areas were found in the center of these accumulations. Spores of *Lycopodium* identical with those described later were seen within the nodules as well as within the giant cells. Because of the superficial resemblance of the lesion to tuberculosis, a section was stained by the Ziehl-Neelsen method. The spores were found to be acid-fast; no tubercle bacilli were found.

CASE 4.—A woman, aged 37, with a history of a cholecystectomy performed three months previously, entered the hospital complaining of pain in the epigas-

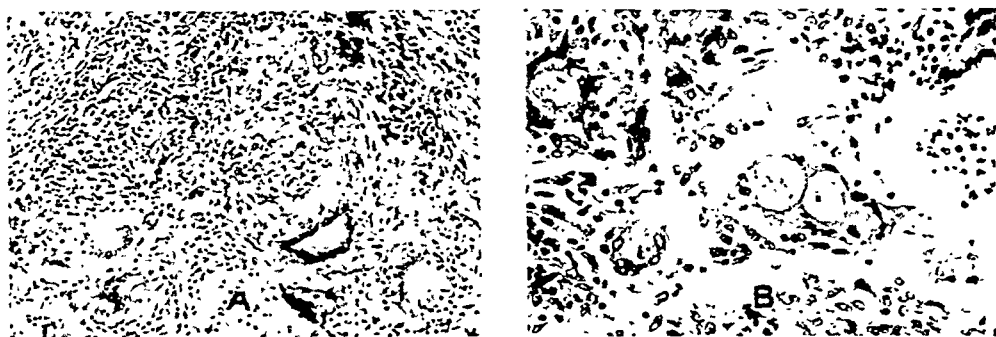


Fig. 1 (case 1).—*A*, the type of reaction; *B*, spores of *Lycopodium* within giant cells.

trium, distention and vomiting. At exploratory laparotomy numerous adhesions were seen, mainly in the right upper quadrant. The visceral and parietal peritoneum were studded by numerous pearly gray nodules, 1 mm. in diameter, many of which were coalescent. These nodules resembled tubercles so much that a diagnosis of tuberculosis of the peritoneum was made. Biopsy showed the lesion to be composed of nodules within which were areas of necrosis surrounded by epithelioid cells, round cells and giant cells of the Langhans type (fig. 2 *A*). The lesion was at first thought to be tuberculous. However, the Ziehl-Neelsen stain was negative for tubercle bacilli, but it revealed one or two acid-fast spores of *Lycopodium* in each of the tubercle-like structures (fig. 2 *B*). A very occasional spore was found within a giant cell. The spores, which stain faintly with eosin, were not visualized in the first routine sections, because they were situated within the necrotic zones. This case illustrated the similarity of these granulomatous nodules to tubercles not only on gross inspection but also on routine microscopic examination with ordinary stains. A similar case has been described by Roth.¹ In that instance, also, a diagnosis of tuberculosis of the peritoneum was made at the time of operation.

1. Roth, H.: Frankfurt. Ztschr. f. Path. 29:59, 1923.

CASE 5.—A Negro with a history of incision and drainage for suppurative adenitis of the neck three months previously, entered the hospital because of a persistent sinus at the site of incision. At operation the sinus tract and adjacent lymph nodes were removed. Microscopic examination of the sinus tract showed a chronic inflammatory process. There were spores of *Lycopodium* among the lymphocytes and also within the giant cells. The lymph nodes showed typical tuberculous adenitis. Ziehl-Neelsen stain demonstrated acid-fast bacilli in the lymph nodes, and spores of *Lycopodium* in the sinus tract. There were also



Fig. 2 (case 4).—*A*, tubercle-like nodules of peritoneum; hematoxylin and eosin stain. *B*, same as *A*, showing acid-fast spores of *Lycopodium* within nodules; Ziehl-Neelsen stain.

crystals of talc in some of the giant cells within the wall of the sinus tract. This case was therefore considered to be one of tuberculous lymphadenitis, complicated by granuloma due to *Lycopodium* and to talc. In this case the spores of *Lycopodium* were most likely only an incidental finding and played no part in the clinical picture. An instance of this nature is represented by the case of de Messer,² who found spores of *Lycopodium* in a squamous cell carcinoma of the forearm in which the *Lycopodium* probably gained entrance through the skin.

2. de Messer, A. F.: *Virchows Arch. f. path. Anat* **163**:111, 1901.

CASE 6.—A man, aged 30, who had had an adenoma of the breast removed, entered the hospital seventeen months later, complaining of numerous tender nodules in the region of the incision. A tentative diagnosis of carcinoma was made. The slides from the original tumor were examined, and no evidence of a malignant condition was found. This patient, however, had had his original operation at a hospital where a dusting powder containing *Lycopodium* was used, so that the possibility of granuloma due to *Lycopodium* was suggested. On removal and examination of the scar, this opinion was confirmed. A picture similar to that in case 3 was found, the spores being contained within the tubercle-like nodules. No tubercle bacilli were found.

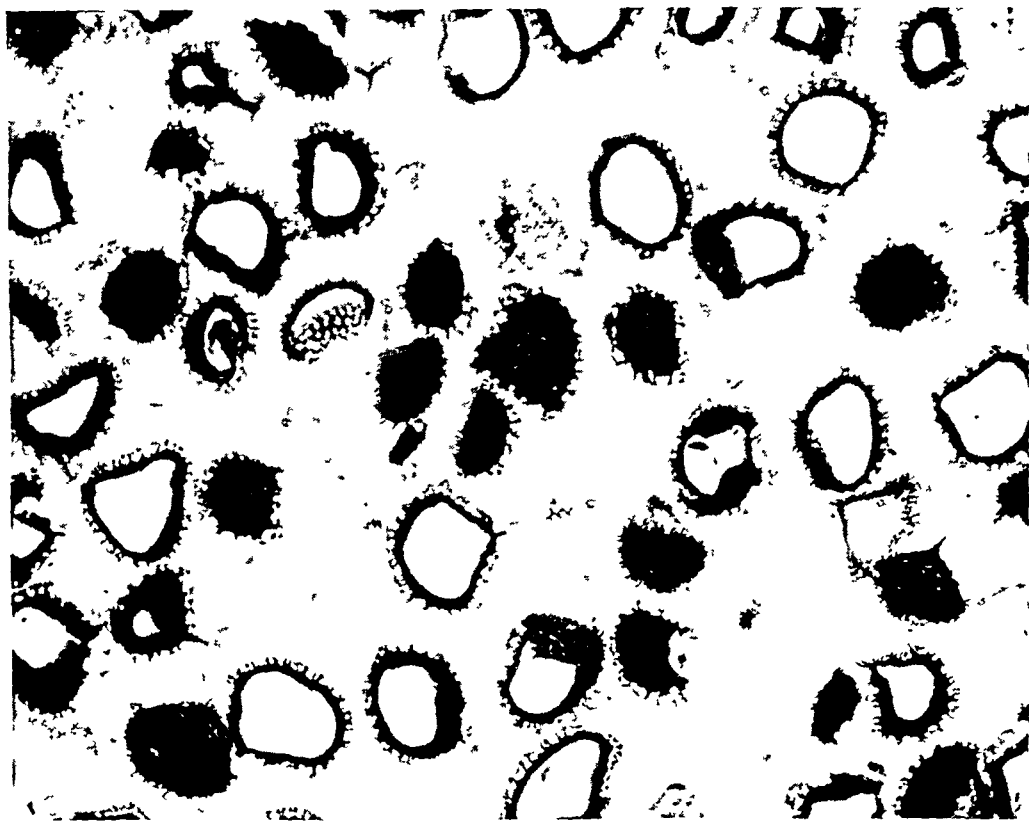


Fig. 3.—Spores of *Lycopodium* in section.

PATHOLOGY OF THE LESION

The lesion is essentially granulomatous, a reaction to the spores of *Lycopodium*. It is composed of granulation tissue, usually in the form of nodules, and contains epithelioid cells and giant cells of the foreign body as well as the Langhans type. There are usually extensive areas of fibrosis and some areas of necrosis. The spores may be seen within the granulation tissue and also within the giant cells themselves. When stained by the ordinary methods they are poorly visualized. However, the Ziehl-Neelsen stain reveals them as acid-fast, bright red, circular bodies, averaging 30 microns in diameter. The contour is scalloped,

and the edges have short spinous processes. Some of the spores are hollow, while others are filled with coarsely granular material. Some show an opening formed by three sides which are also covered with spinous processes. Reconstruction in three dimensions reveals the spores to be irregularly spheroidal bodies of a nodular mulberry appearance, covered with spinous projections (fig. 3). No change is noted in their morphology after treatment with weak acids or bases.

COMMENT

Lycopodium, because of its fine spicules, has a tendency to become adherent to any tissue on which it is deposited, and on manipulation it may be forced beneath the surface. It is therefore possible for an operative specimen to become contaminated with spores of *Lycopodium* during removal. To demonstrate this, the freshly removed specimen from a patient operated on for acute appendicitis was intentionally handled with gloves which had been powdered with these spores. After the specimen had been dehydrated, embedded, sectioned and stained, microscopic examination revealed many of the spores completely embedded within the tissue. It is obvious that this may lead to an error in diagnosis. To avoid such an error it is necessary that the spores be found within giant cells or within a granulomatous lesion. This was the case in all of the instances recorded here.

Animal inoculation with the spores of *Lycopodium clavatum* resulted in the formation of granulation tissue after from two to six weeks, which on microscopic examination was not unlike the reaction in man, including the presence of the spores within the giant cells. Further experimental studies on the various phases of this problem are in progress. No attempt will be made in this paper to review the extensive literature on experimental lesions produced by *Lycopodium*.

It is also possible that the crystals of magnesium silicate (talc) produce such lesions. This idea obtains support in the finding of the crystals within the giant cells in the fistulous tract in case 5.

The following case demonstrates the formation of minute talc granulomas in an otherwise normal appendix.

CASE 7.—A man, aged 34, had had an operation for volvulus of the sigmoid eight years previously, and one for separation of adhesions with resection of the sigmoid eight months previously. During the present hospitalization, an appendectomy was performed and an apparently normal appendix removed. On microscopic section, granulomas were observed in the serosa; and within giant cells there were present refractile bodies morphologically identical with the crystals of talc.

SUMMARY

Granulomatous lesions grossly resembling tuberculosis or neoplasm and resulting in the formation of persistent sinuses may be produced

by the surgical use of dusting powders containing as an ingredient spores of *Lycopodium*.

Macroscopically and microscopically, the lesions may be confused with those of tuberculosis; however, the Ziehl-Neelsen stain shows the presence of the acid-fast spores of *Lycopodium*.

The spores can be considered the causative agents of such lesions only when found within giant cells or within granulomatous nodules.

These spores should not be used as an ingredient of dusting powders which come in contact with open wounds.

Similar granulomatous lesions may also be caused by talc.

LEIOMYOMA OF THE PROSTATE

REPORT OF THREE CASES

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AND

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Overgrowth of the epithelial components of the prostate is usually accompanied by overgrowth of the fibromuscular stroma. However, neoplastic proliferation of the stroma alone is rare. A review of the available literature yielded records of only eight cases of leiomyoma of the prostate. During the past year, solitary myomatous nodules were observed in three of the prostates received in the Laboratory of Surgical Pathology of the New Haven Hospital. A report of these cases with a brief review of those previously described is presented here.

REPORT OF CASES

CASE 1.—A 59 year old man was admitted to the New Haven Hospital (Dr. Deming's service) on July 20, 1932, complaining of frequency, burning and pain on urination of three or four years' duration. He stated that during part of this time he was treated for cystitis, and that beginning about one month before admission there developed a sense of fulness above the pubis, hesitancy, dribbling, occasional incontinence and inability to empty the bladder completely. No history of venereal disease was obtained.

On admission he appeared to be in fairly good condition. The systolic blood pressure was 188 mm. of mercury, and the diastolic 100 mm. The external genitalia showed nothing unusual except a small left hydrocele. On rectal palpation the prostate was not tender, and it appeared moderately firm and symmetrically enlarged to about two and a half times its usual size. The median groove and furrow were absent. With a catheter 1,000 cc. of urine was obtained and immediately replaced by sterile physiologic solution of sodium chloride. The urine contained a few white blood cells, and no albumin or sugar. The bladder was then slowly decompressed by an inlying catheter. The phenolsulphonphthalein excretion was 45 per cent in two hours. The nonprotein nitrogen of the blood was 118 mg. per hundred cubic centimeters. Five days later (July 25) it was 43 mg. Cystoscopic examination on August 2 revealed a solitary large calculus in the bladder, several small diverticula in the fundus of the bladder and enlargement of both lateral lobes and the median lobe of the prostate. The following day the calculus was removed through a suprapubic cystostomy, and a bilateral vasotomy was performed. The calculus measured 2 cm. in diameter and had the shape of a jackstone. Following the operation the patient continued to have an elevation of temperature to between 100 and 101 F. On September 1, signs of

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pneumonia developed in the right lung, accompanied by a further rise in temperature to between 102 and 103 F. During the next two weeks he received several blood transfusions, and his condition improved so that after September 16 he was out of bed most of the time. On September 28, a suprapubic prostatectomy was performed by Dr. P. W. Skinner. Following the operation the patient's condition steadily improved, and he was discharged on October 25 in good condition.

Description of Specimen.—Of the five pieces of firm gray tissue, varying in size from 2 by 1 by 0.5 to 4 by 3 by 1.5 cm., one was roughly globular and firmer than the rest. It measured 2 cm. in diameter, and on cut section had a whorled appearance of interlacing bundles and a watered-silk luster. While no glandular

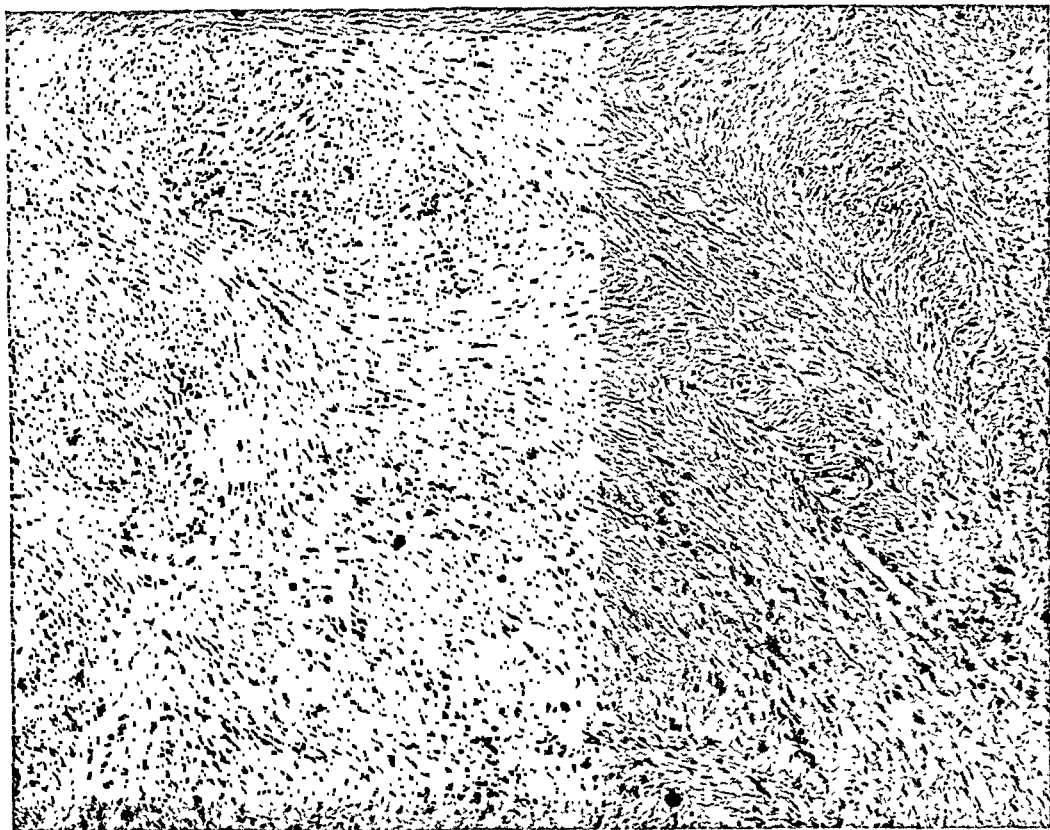


Fig. 1.—Leiomyoma of the prostate in a 65 year old man (case 2). The interlacing arrangement of the smooth muscle bundles is shown; $\times 100$.

tissue could be made out grossly in this nodule, this was quite evident in the other pieces. In microscopic preparations the nodule was surrounded by a fibrous connective tissue capsule and was composed of interlacing smooth muscle bundles and no glandular elements. In sections stained by the methods of Mallory (aniline blue) and of van Gieson, a delicate network of fine connective tissue fibrils was seen between the muscle bundles. The other pieces of tissue showed glandular overgrowth and an increase of the fibromuscular stroma.

CASE 2.—A 65 year old night watchman was admitted to the New Haven Hospital (Dr. Deming's service) on Aug. 9, 1932, complaining of hesitancy, frequency, dribbling and burning on urination and occasional incontinence. His symptoms had begun thirty years before, but had increased in severity during the

last two years. He was now voiding hourly and complained of inability to empty the bladder completely. No history of venereal disease was obtained.

On admission he was semistuporous. The systolic blood pressure was 140 mm. of mercury and the diastolic 70 mm.; the pulse rate was 84 per minute and the temperature 99.5 F. The external genitalia appeared normal except for bilateral, easily reducible inguinal hernias. On rectal palpation the prostate was not tender, was of rubbery firmness and was symmetrically enlarged to a moderate degree.

The day following admission signs of bronchopneumonia developed, but the patient recovered. On August 19, the phenolsulphonphthalein excretion was from 55 to 60 per cent in two hours. The nonprotein nitrogen of the blood was 47 mg. per hundred cubic centimeters. Ten days later it was 31 mg. per hundred cubic centimeters. Cystoscopic examination on that day (August 29) revealed numerous small diverticula in the bladder and a diffuse enlargement of the prostate. On August 30, a perineal prostatectomy and bilateral vasotomy were performed by Dr. P. W. Skinner. Following the operation the wound healed slowly. On September 28, a recto-urethral fistula developed which healed spontaneously in about two weeks. The perineal wound was still draining slightly when the patient was discharged on November 17, but ceased draining by December 6.

Description of Specimen.—A smooth rounded nodule was attached to one of the six pieces of prostatic tissue varying in size from 1.5 by 1 by 1 to 3 by 2 by 1 cm. The nodule measured 12 mm. in diameter, was firmer than the rest of the tissue, and had a uniform grayish-white whorled appearance on the cut surfaces. The other pieces had a glandular structure. In microscopic preparations the nodule was composed of interlacing smooth muscle bundles in an abundant fibrous connective tissue stroma (fig. 1). This structure was clearly brought out in preparations stained by the method of van Gieson. The nodule of smooth muscle tissue was sharply demarcated from the surrounding glandular tissue, although no definite connective tissue capsule could be made out. Preparations from the other pieces showed enlarged prostatic acini embedded in an abundant fibromuscular stroma. Some of the lumens of the acini were lined by columnar cells; others appeared distended and lined by low cuboidal epithelium. An infiltration with small round cells was noted in some areas of the stroma.

CASE 3.—A 67 year old man was seen by Dr. Alfred C. Carpenter of Milford, Conn., early in 1932. At this time the patient complained of urinary difficulty of about four years' duration, consisting of marked straining in starting the urinary stream and of some dribbling after urination. No history of venereal disease was obtained.

On rectal palpation the prostate was slightly enlarged, hard and not tender. A catheter (no. 20 French) was passed without difficulty. No residual urine was obtained. Subsequently urination gradually became more difficult. When seen in February, 1933, the patient stated that for the previous six months he had to void hourly and was unable to empty the bladder completely. Dribbling also increased. He complained of no pain at any time and appeared to be in good general health. At this time further enlargement of the prostate, in the middle lobe only, was noted on rectal palpation. The residual urine amounted to about 250 cc. On February 24, a suprapubic cystostomy, and on March 12, a prostatectomy, were performed by Dr. Carpenter. The patient made a good recovery. All wounds were healed when the patient was discharged on April 11.

Description of Specimen.—The specimen consisted of a roughly Y-shaped mass of prostatic tissue, measuring approximately 5 by 5 by 2 cm. The arms of the Y represented portions of the lateral lobes and the base of the Y, the enlarged



Fig. 2.—Drawing of a sagittal section through the prostate of a 67 year old man (case 3). The round encapsulated leiomyomatous nodule has a characteristic whorled appearance.



Fig. 3.—Leiomyoma of the prostate (case 3). The interlacing smooth muscle bundles forming the tumor are surrounded by a definite fibrous connective tissue capsule; $\times 12$.

median lobe. The enlargement of the median lobe was symmetrical and spherical. This portion was firmer than the lateral lobes. A sagittal section of the specimen (fig. 2) revealed a circumscribed, round, encapsulated mass of firm tissue, 2 cm. in diameter, with a whorled appearance and a grayish-white, watered-silk luster. No glandular tissue could be seen within this nodule. Sections through the lateral lobes showed masses of glandular tissue. In microscopic preparations the nodule in the median lobe was seen to be composed of interlacing bundles of smooth muscle in a delicate fibrous connective tissue stroma. This was particularly well seen in preparations stained by the method of van Gieson. The nodule was surrounded by a well developed and complete fibrous connective tissue capsule (fig. 3). Endothelial lined vascular channels were numerous throughout. No glandular elements were present. The adjacent tissue and the lateral lobes were composed of small masses of glandular tissue embedded in a dense fibromuscular stroma. The glands varied considerably in size and shape. Their lining epithelium was tall columnar, and there were numerous papillary infoldings of the mucosa. In others the lumens were distended and the lining epithelium flat.

CASE REPORTS FROM THE LITERATURE

LEBEC'S¹ CASE.—The first case of leiomyoma of the prostate was presented before the Société Anatomique in Paris at its meeting on Feb. 18, 1876, by Lebec. The patient was a 76 year old man, admitted to the Hôtel Dieu (Guérin's service) on Jan. 5, 1876, with urinary retention. He complained of no pain except that caused by distention of the bladder. Difficulty was encountered in introducing a metal sound, but a soft rubber catheter passed easily, and 1.5 liters of clear urine was obtained. After this the patient was catheterized three times daily, and pus soon appeared in the urine. The patient died of pneumonia on January 15. At necropsy, the urinary bladder was enlarged and trabeculated, and it contained two small calculi. The prostate measured 5.5 cm. transversely and 6 cm. longitudinally, and the length of the distorted prostatic portion of the urethra was 10.5 cm. Superimposed on the median lobe there was a circumscribed tumor nodule which shelled out easily. Microscopic examination showed it to be composed of smooth muscle fibers resembling those of the uterus.

DAMSKI'S² CASE.—The second case of leiomyoma of the prostate was reported by Damski, from Russia, in 1924. The patient, a 62 year old farmer, complained of a visible swelling in the perineal region, causing marked difficulty and pain on defecation. He had no urinary symptoms. In the perineum a little to the right of the midline, near the anus, there was a walnut-sized swelling. On rectal palpation a voluminous, smooth, spherical and not tender tumor was felt at the site of the prostate. The upper margin of this could not be reached. On cystoscopic examination there was no residual urine; the bladder appeared normal except for some reddening and edema of the trigone. Examination of the urine gave negative results. The tumor was removed piecemeal by a perineal approach. The patient, when discharged eighteen days later, was free from symptoms. The removed pieces of tissue were grayish white and weighed 180 Gm. Microscopic preparations from many parts of the tumor showed it to be composed entirely of smooth muscle tissue.

1. Lebec: *Progrès méd.* 4:471, 1876.

2. Damski, A.: *Ztschr. f. urol. Chir.* 16:47, 1924.

BUGBEE'S³ CASE.—Bugbee, in 1926, reported a leiomyoma of the prostate in a 49 year old man, who was admitted to the St. Luke's Hospital in New York on May 24, 1925, with complete retention of urine. The patient's urinary symptoms commenced about two weeks previous to admission, when he began to have a poor stream and a tendency to dribble. On the day before admission he was unable to void and was catheterized. On rectal palpation the prostate appeared symmetrically enlarged. The right lobe felt softer than the left, and there was slight induration over the left lobe. A catheter was introduced and left in place for the next seven days, during which the patient's temperature ranged between 99 and 101 F. At this time tenderness, softening and fluctuation were felt over the left lobe on rectal palpation. With the object of draining the abscess an external urethrotomy was performed. A mass of soft friable material extending well beyond the reach of the finger filled the space between the bladder and rectum. About 12 ounces (340 Gm.) of this material was removed. Microscopic examination of the fragments showed them to be composed of smooth muscle tissue. The patient lost 30 pounds (13.6 Kg.) in weight. He received roentgen therapy over a period of four months. Since then his condition had slightly improved. The perineal wound opened several times, with a temporary leakage of urine. The suprapubic drainage was maintained.

RUBRITIUS'⁴ CASE.—Rubritius, in 1927, reported the case of a 70 year old man who for some time had had incomplete retention of urine. The residual urine amounted to 400 cc. The prostate was "the size of a tangerine," moderately firm and smooth. Through a suprapubic cystotomy, a mass about the thickness of two thumbs protruded 8 cm. into the bladder, encircling about three fourths of the urethral orifice. The mass shelled out easily and consisted of several nodules. On microscopic examination it was seen to be composed of interlacing bundles of smooth muscle. At the periphery of a nodule glandular prostatic tissue was present in a few places.

WOLMAN'S⁵ CASE.—Wolman, in 1931, reported the case of a 73 year old merchant, who entered the Pennsylvania Hospital on Aug. 31, 1929, complaining of urinary retention, frequency, which was more marked at night, pain in the region of the bladder and loss of weight. These symptoms had increased in severity since their onset fourteen months previously. On examination a large intra-abdominal tumor was discovered and enlargement of the prostate noted. An indwelling catheter was inserted and allowed to remain. The patient became progressively weaker and emaciated and died of cachexia and terminal lobular pneumonia on October 29. At necropsy, a "histioid tumor" arising in the left kidney and metastasizing to the mesentery, retroperitoneum, spinal column and liver was found. The bladder was contracted and had thick trabeculated walls. A rounded firm nodule projected into the bladder. On section this nodule was encapsulated, glistening and pearly white, with whorls of fine fibers. Microscopic preparations showed it to be composed of smooth muscle cells with scanty connective tissue stroma. The tumor was surrounded by prostatic tissue except at its superior pole, where it lay directly beneath the bladder mucosa. No glandular elements were seen in the tumor.

3. Bugbee, H. G.: *J. Urol.* **16**:67, 1926.

4. Rubritius: *Ztschr. f. urol. Chir.* **24**:418, 1928.

5. Wolman, Irving J.: *J. Urol.* **25**:93, 1931.

HINMAN and SULLIVAN'S ⁶ CASES.—Hinman and Sullivan, in 1931, reported two cases of leiomyoma of the prostate. The first patient, a 36 year old man, complained of sharp pain in the rectum with a desire for defecation, occasional aching discomfort in the perineum, slight burning on urination and some nocturia. These symptoms had been present for about one year. One year prior to the onset of these symptoms he was told by a physician that the median lobe of the prostate was enlarged. He also had a gonorrheal infection for ten years with recurrent discharge and urethral stricture. On rectal palpation a smooth, rounded, elastic mass was felt. The prostatic furrow and notch were obliterated by the mass. The tumor, removed by a perineal approach, was attached by a narrow pedicle to the prostate near its apex. The underlying prostatic surface was smooth and apparently intact. The tumor mass, when removed, measured 2.5 by 3.5 by 4.5 cm., and had a thin fibrous capsule. On the cut surfaces it exposed interlacing fibromuscular strands. Microscopic preparations showed the tumor to be composed of interlacing strands of smooth muscle through which ran rather large vascular channels. No epithelial elements were noted.

The second patient was a 39 year old man who was admitted to the United States Naval Hospital, Mare Island, on Jan. 13, 1931, complaining of extreme constipation, burning and tenderness in the rectum, aggravated by defecation. The symptoms had begun six months previously, and had increased steadily in severity. His only urinary complaint was nocturia for several years. On rectal palpation a firm, elastic tumor mass, about the size of a baseball, was felt over the prostatic area. The normal markings of the prostate were obliterated. About two thirds of the tumor had been removed by a perineal approach when the patient went into shock. He died the next day. The portion of the tumor removed measured 2 by 2 by 3 cm., and weighed 5 Gm. and was firm and elastic. The cut surfaces exhibited a whorl formation suggestive of a leiomyomatous growth. Microscopic preparations showed irregular bundles of smooth muscle cells supported by fibrous connective tissue.

DEUTICKE'S ⁷ CASE.—The most recent report of a case of leiomyoma of the prostate came from Vienna and was made by Deuticke, in 1932. The patient was a 65 year old head-forester, who complained of difficulty in passing stools for the previous two months. In spite of a strong desire for defecation he had no stools for days at a time, and only by taking strong cathartics and by hard and exhausting bearing down could he pass any. He complained of no urinary difficulty. On rectal palpation a large, firm, hardly movable, globular tumor with a lobular surface compressed the rectum just above the sphincter. The tumor occupied the prostatic region and did not involve the rectal wall. Cystoscopic examination revealed a few cubic centimeters of residual urine, slight trabeculation of the bladder, elongation of the prostatic portion of the urethra and marked enlargement of the prostate, particularly on the right. The nonprotein nitrogen of the blood was 37.8 mg. per hundred cubic centimeters. The tumor, which was "the size of a man's fist," was shelled out in globular masses by a perineal approach. On microscopic examination all these grayish-white masses proved to be composed of smooth muscle tissue. In preparations stained by the method of van Gieson scanty connective tissue was seen between the interlacing muscle bundles. No epithelial elements were noted. The patient had no symptoms when discharged three weeks following admission.

6. Hinman, Frank, and Sullivan, J. J.: *J. Urol.* **26**:475, 1931.

7. Deuticke, Paul: *Deutsche Ztschr. f. Chir.* **236**:475, 1932

COMMENT

Only eleven cases of leiomyomas of the prostate are available for analysis. Depending on size, location and concomitant changes in the prostate, they produced disturbances either of urination or of defecation. Seven of the patients (those of Lebec, Bugbee, Wolman, Rubritius and us) had urinary symptoms only. The remaining four (patients of Damski, Hinman and Sullivan and Deuticke) had primarily rectal manifestations.

In most of the patients with urinary symptoms the presence of the myomatous nodule perhaps only exaggerated the disturbances due to enlargement of the rest of the prostate. In none of these could the urinary difficulties be attributed to the myomatous growth alone, although the growth arising in the prostate proper (mostly in the median portion) contributed to the distortion of the urethra.

In the group of patients with rectal disturbances, the tumor obviously produced obstruction. Arising in the posterior portion of the prostate, it grew toward the rectum.

The location of these leiomyomas with respect to the prostate and the surrounding organs suggests a genetic difference in the tumor anlage. However, the information thus far available is insufficient to ascertain the validity of this suggestion.

HYPERTENSION WITH RETROPERITONEAL GANGLIO- NEUROMA AND SOFTENING IN BRAIN AND SPINAL CORD

REPORT OF A CASE IN A YOUNG MAN

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The region of the suprarenal glands is a common site for the occurrence of a group of neurogenic tumors classified as sympathogoniomas, ganglioneuromas and paragangliomas. These tumors have the same embryologic origin as the suprarenal medulla and the adjacent sympathetic ganglions, namely, the primitive sympathogonia which wander into this region. Divergence in the process of differentiation leads to variation in structure and in function.

The most primitive type of tumor in this group is the sympathogonioma (neurocytoma). It is composed of small round cells, about the size of a small lymphocyte, each containing a deeply staining, round, compact nucleus and a scanty amount of cytoplasm. The paraganglioma (pheochromocytoma) is a more mature type of tumor composed of chromaffin cells resembling those of the suprarenal medulla. These large cells are polyhedral. In sections fixed in Zenker's solution the cytoplasm contains characteristic brown granules. The nuclei are large, stain poorly, are very granular and contain one or two nucleoli. The ganglioneuroma is a still more mature neoplastic representative of the primitive stem cell in its divergence and maturation in the direction of the spinal ganglion type of cell.

Paragangliomas have been found in cases of hypertension, and an etiologic rôle in its development has been suggested.

The case reported here is that of a young man who had a high blood pressure in the presence of a ganglioneuroma in the vicinity of the left suprarenal gland.

REPORT OF CASE

On May 2, 1932, a white man, aged 23, entered Passavant Memorial Hospital in the service of Dr. M. H. Barker. He complained of paralysis of the right side of the body, inability to urinate, intermittent pain in the left arm, blindness in the left eye and ringing in the ears.

The illness began six weeks previous to admittance, with pain in the right shoulder and numbness in the forearm and hand. Within a short period of time the arm became paralyzed. Two weeks later pain and numbness were noticed in the left leg. The muscles of speech were also affected. On April 26, the patient

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suddenly became unable to urinate. Ringing in the ears had been present intermittently for a week prior to this time. Throughout his life he had had repeated attacks of sharp pains in the abdomen, short in duration and with no relation to meals or defecation.

The past history included tonsillitis, rheumatic fever, scarlet fever and measles. These diseases had no known sequelae. Four years prior to the illness in question he was said to have had meningitis, but the condition was later diagnosed as encephalitis. One year later he complained of failing vision, which was thought to be due to arteriosclerosis.

The patient was poorly nourished, with an apparent right facial paralysis and defective speech. Spastic paralysis of the right arm and flaccid paraplegia with anesthesia of the legs and decreased sensation up to the umbilicus were present. The blood pressure ranged from 250 systolic and 120 diastolic to 274 systolic and 140 diastolic; the temperature was 99.6 F., and the pulse rate, 100. Ophthalmoscopic examination revealed marked arteriosclerosis of the retinal vessels and evidences of old retinal hemorrhage. Vision was absent in the left eye and was only 2/5 in the right. The heart was enlarged to the left.

The urine contained casts, erythrocytes and leukocytes. The red blood count was within normal limits, while the white count varied from 13,000 to 15,000. The spinal fluid was normal. Phenolsulphonphthalein excretion after intramuscular injection was from 25 to 30 per cent in two hours. Blood cultures before death showed a growth of *Bacillus coli-communior*.

On May 24, generalized convulsions suddenly developed, the patient vomited, had incontinence of feces and died.

Postmortem Examination.—The heart weighed 500 Gm. All of the valves were essentially normal. The maximum thickness of the wall of the left ventricle was 30 mm.

Thirty per cent of the intima of the right coronary artery and less of the left showed yellow thickening. Atherosclerosis involved from 95 to 100 per cent of the intima of the aorta below the renal arteries. The vertebral and basilar arteries and also the branches of the circle of Willis showed marked yellow thickening of the intima and stood wide open when cut.

The right kidney weighed 210 Gm. The capsule stripped rather easily, leaving a fairly smooth surface with reddish-brown, slightly elevated areas from pinpoint size to that 12 by 30 mm.; several of these had yellow centers. Numerous red bands from 1 to 2 mm. in width extended through the entire renal cortex. Everywhere the normal cortical markings were absent or indistinct. The left kidney answered essentially to the same description as the right.

The brain was sectioned in the coronal plane and showed areas of yellow softening as follows: (1) immediately anterior to the optic chiasm and in the center of the corpus callosum, 5 by 6 mm.; (2) in the head of the left caudate nucleus, involving about one-half the width and two-thirds the length of the left internal capsule, 8 by 15 mm.; (3) in the plane just anterior to the cerebral peduncles, involving the left optic thalamus, the internal capsule and a part of the lenticular nucleus (both putamen and globus pallidus), 7 by 15 mm.; (4) in the plane immediately posterior to the cerebral peduncles, in the white matter just lateral to the lenticular nucleus, 5 by 6 mm.

Near the lower pole of the left kidney and attached to it by means of fibrous tissue and blood vessels was a round, well encapsulated mass 4 cm. in diameter. Its cut surface was moist and pale yellowish brown. A grating sensation was felt when a knife-blade was scraped over it. A cord of tissue 5 mm. in diameter extended from this mass of tissue to the left testicle.

The gallbladder contained about one hundred round black stones from 1 to 2 mm. in size. Its wall measured from 2 to 5 mm. in thickness.

The remaining organs showed little or no gross pathologic change.

The anatomic diagnosis was: multiple areas of softening in the brain; organized hemorrhagic softening in the posterior columns of the lumbar segments of the spinal cord; ganglioneuroma of the region of the left kidney; concentric hypertrophy of the heart; arteriosclerosis of the coronary arteries and of the arteries at the base of the brain; moderate thickening of the aortic and mitral



Fig. 1.—Photomicrograph of lower lumbar cord showing area of softening in posterior columns and the masses along each posterior nerve root.

valves; atheromatosis of the aorta; arteriosclerotic contracted kidneys; acute focal (descending) purulent and hemorrhagic nephritis; acute hemorrhagic pyelitis and cystitis; slight bilateral bronchopneumonia; bullous emphysema of the right lung; chronic cholecystitis, and cholelithiasis.

Microscopic Examination.—Microscopic examination of the various organs confirmed the anatomic diagnosis. Sections of the left testis revealed no mature spermatozoa. The smaller arteries and the arterioles in all organs examined had thickened hyaline walls and narrowed lumens. This change was most marked in the vessels of the kidneys, brain and spinal cord.

Some of the ganglion cells of the anterior horns in the lower portion of the spinal cord stained diffusely with hematoxylin, and the nuclei were indistinct. Occupying the central part of the posterior portion of the cord and close to the central canal, there was a fairly well circumscribed, pale, oval mass (fig. 1). The central part of this mass was necrotic and composed of granular material irregularly distributed in a fine fibrillar meshwork. Near one margin there was an area of hemorrhage. In the periphery of the mass there were numerous large round cells filled with brownish-yellow pigment. Outside the spinal cord along the posterior nerve roots were two rounded nodules about the size of the lower power field of

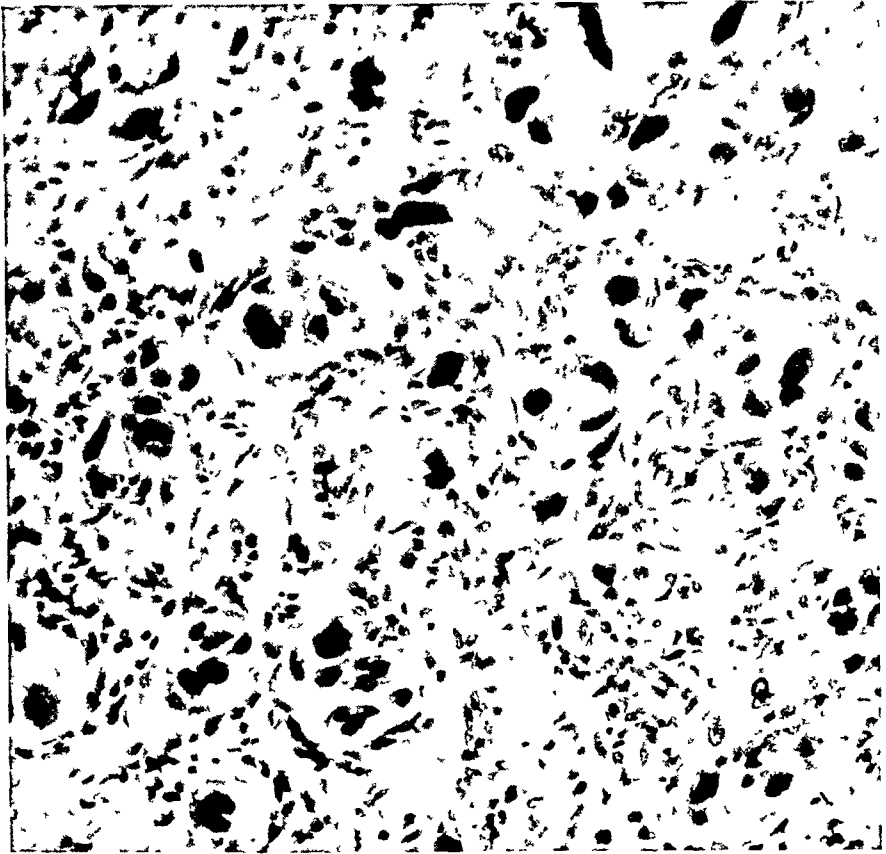


Fig 2.—Photomicrograph of the tumor showing the various cell types described in the text; $\times 190$.

a microscope. The central portion of one of these nodular masses was necrotic and contained brownish-yellow, granular pigment, much of which was intracellular. The peripheral portion of this mass was composed of round and elongated cells with a fibrillar network. The mass was enclosed in a sort of capsule, composed in part of connective tissue and along one side of what appeared to be nerve fibers. The nodule on the opposite posterolateral portion of the cord was composed of small round and oval cells in an abundant intercellular fibrillar material. The histologic picture of this organized hemorrhagic softening suggested an approximate age of 4 weeks.

The tumor near the left kidney was surrounded by a thick capsule of connective tissue from which septums passed into its substance. The parenchymatous elements

of the tumor consisted of cells, to be described later, which for the most part were arranged in the form of indistinct nests and cylindric cords (fig. 2). However, an occasional cell could be found isolated. The stroma consisted of connective tissue; some of it contained collagen but most of it was argentophil. Numerous thin-walled and malformed blood vessels coursed throughout the tumor. In some of the vessels the intima showed a moderate degree of fibrosis, while in others the lumens had been practically obliterated. One vessel contained a calcified thrombus. The aforementioned nests of cells were composed of three general types. The less numerous type of cell had a rather compact nucleus and a small amount of cytoplasm. In the second type the nucleus stained less deeply and was almost vesicular, while the cytoplasm was more abundant. The third group of cells, which were in the majority, resembled somewhat those of a spinal ganglion. Generally they were multipolar, and each contained one or more large nuclei. The chromatin material was arranged in fine granules and skeins, or infrequently was collected for the most part in one or more nucleoli. Generally two or more of the cells or infrequently a single cell was enclosed in a capsule of argentophil connective tissue. The nerve fibers within the tumor were nonmedullated.

The cord of tissue which connected the tumor with the left testicle consisted chiefly of many blood vessels in a fibrous stroma. The intima of some of the arteries had undergone marked fibrosis.

COMMENT

Ganglioneuromas arise from cells which migrate from the neural crest during embryonic life. These undifferentiated sympathogonia may form mature chromaffin tissue or they may give rise to sympathetic ganglion cells. At any point in the process of differentiation of these cells, tumors may arise. The cellular architecture of the tumors can therefore be representative of any of the developmental stages through which the cells pass in their process of maturation. Cases of ganglioneuroma and paraganglioma occurring in the region of the suprarenals have been reported from time to time. Bigler and Hoyne,¹ in 1932, reviewed the literature on ganglioneuroma and collected reports of ninety-seven cases. Haven and Weil² have since added a report of a case of multiple ganglioneuroma. Eisenberg and Wallerstein³ collected reports of fifty-three cases of paraganglioma and reported one of malignant paraganglioma arising from the suprarenal medulla. Oppenheimer and Fishberg,⁴ in 1924, could find no records of ganglioneuroma associated with hypertension. A review of the literature since 1924 likewise failed to reveal such an association.

Paraganglioma, on the other hand, especially that originating in the suprarenal glands, has been found associated with hypertension without

1. Bigler, J. A., and Hoyne, Archibald: *Am. J. Dis. Child.* **43**:1552, 1932.

2. Haven, Hale, and Weil, Arthur: *Arch. Path.* **13**:713, 1932.

3. Eisenberg, A. A., and Wallerstein, Harry: *Arch. Path.* **14**:818, 1932.

4. Oppenheimer, B. S., and Fishberg, A. M.: *Arch. Int. Med.* **34**:631, 1924.

any other discoverable etiologic factor (Mayo,⁵ Oppenheimer and Fishberg,⁴ Pincoffs,⁶ and Vaquez, Donzelot and Geraudel⁷).

Some paragangliomas are composed of epinephrine-bearing tissue, while ganglioneuromas do not contain such elements. One may conclude, therefore, that in spite of the origin of these two tumors from a common primitive type of cell, when hypertension is associated with ganglioneuroma it is merely coincidental. It is believed that the hypertension in this case can best be explained on the basis of the renal and generalized vascular changes.

SUMMARY

A case of hypertension in a young man is reported. A small ganglioneuroma, histologically moderately mature, was found in the retroperitoneal region, near the left kidney.

Marked arteriosclerosis was present in the kidneys, brain and spinal cord. The brain and spinal cord showed multiple areas of hemorrhagic softening. There was moderate arteriosclerosis in the heart with mild involvement of the arterioles of the lungs, liver, suprarenal glands, pancreas, intestines and skeletal muscles. The left testis was maldeveloped.

Although hypertension not otherwise explainable has been observed associated with a type of tumor embryologically related to the tumor in this case, the high blood pressure in this patient can probably be explained best on the basis of the vascular and renal changes. The presence of the ganglioneuroma was most likely only coincidental.

5. Mayo, C. H.: J. A. M. A. **89**:1047, 1927.

6. Pincoffs, M. C.: J. A. M. A. **93**:63, 1929.

7. Vaquez, H.; Donzelot, E., and Geraudel, E.: Presse méd. **37**:169, 1929.

EXAMINATION OF PATHOLOGIC TISSUE BY FILTERED ULTRAVIOLET RADIATION

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Ultraviolet rays have been used extensively in many scientific fields. In the medical branches considerable application has been made in clinical dermatology. Ultraviolet radiation has been applied, to some degree, in the gross examination of normal tissues, but in the investigation of pathologic material it has had limited application.

The source of ultraviolet radiation may be a mercury vapor, carbon arc or cold quartz lamp. In our studies we used a mercury vapor arc lamp. In order to procure a maximal fluorescent effect, the radiation, consisting of longer and shorter waves, should be filtered through a nickel oxide filter. This permits the selection of waves ranging from 300 to 400 millimicrons in length (with the greatest spectral intensity at 366 millimicrons). The examination of pathologic material must be performed either in a dark room or in a dark hood. Water-washed specimens, either fresh or fixed in a dilute solution of formaldehyde, U. S. P. (1:10), will, when examined by ultraviolet radiation, emit secondary visible rays; this phenomenon is called fluorescence. If a specimen has been fixed in a dilute solution of formaldehyde for five or more days, it loses the optimal fluorescent effect; under such circumstances the removal of a thin slice of tissue will restore the maximal fluorescence.

The study of normal tissues by filtered ultraviolet radiation is reviewed thoroughly in Danckwortt's¹ monograph. Knowledge of the fluorescence of normal tissue is helpful in undertaking the investigation of pathologic tissue. Compact mature cortical bone fluoresces a light blue to a yellow-white, depending on compactness; this is apparently related to the ratio of inorganic to organic substances. Articular cartilage in the young fluoresces a uniform light blue, contrasting strongly with the opaque yellow-white of articular cartilage of adults. Subcutaneous or abdominal fat emits a clear yellow fluorescence. Muscle varies from a light tan to a dark brown, probably depending on the blood content. The various connective tissues fluoresce differently,

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Aided by the Emanuel Libman Fund.

1. Danckwortt, P. W.: *Lumineszenz-Analyse im filtrierten ultravioletten Licht*, Leipzig, Akademische Verlagsgesellschaft, 1929.

depending on consistency and cellularity; the more cellular connective tissues fluoresce purple-brown, whereas dense acellular connective tissue, such as tendon, fluoresces white.

As stated, little work has been done with pathologic tissues. Körbler² recently reported on the examination of three pathologic breasts; Kramer³ described the appearance of four specimens; Policard⁴ studied an experimental rat sarcoma and noted that the center of the tumor was a brilliant red (it was surrounded by a narrow zone of dark violet, which was again encircled by a white periphery). This red fluorescence is characteristic of hematoporphyrin; its presence in tumors is considered to be a result of bacterial infection. Körbler² mentioned the red fluorescence of carcinomatous ulcers, superficially located. A red fluorescence has been noted in a wide variety of conditions, and is not specifically indicative of tumor.

Our own experience includes a study of over five hundred specimens from postmortem and surgical material. In most, an opportunity of correlating the gross and microscopic findings with the fluorescent appearances was afforded. Our interest was centered mainly on the examination of tumors, especially of bone.⁵

The examination of any tissue or organ by filtered ultraviolet radiation resolves that tissue or organ into its constituent elements. It is a macroscopic method of differentiating the various components of a specimen through variation in fluorescence. The colors evoked are not necessarily specific, since tissues of various natures may sometimes emit approximately the same fluorescence (both tendons and mature bone fluoresce in shades of white). This is an important point and should be stressed. However, after experience, a particular type of tissue may be usually recognized by its fluorescence with ease, and minor variations therefrom may be readily interpreted. The variations in color probably depend on both inorganic (as in bone) and organic (as in fat) constituents, and on both intracellular (as in carcinomas) and extracellular (as in tendon) material. In this connection, variations in the inorganic content of nuclei and of cytoplasm in different carcinomas were reported by Scott and Horning.⁶

Furthermore, with filtered ultraviolet radiation areas not well demarcated under natural light are clearly visualized. Areas which

2. Körbler, J.: *Strahlentherapie* **41**:510, 1931; **43**:317, 1932.

3. Kramer, K.: *Virchows Arch. f. path. Anat.* **274**:215, 1929.

4. Policard, A.: *Compt. rend. Soc. de biol.* **91**:1423, 1924; *Bull. d'histol. appliq. à la physiol.* **5**:266, 1928.

5. This formed the basis of an exhibit at the Post-Graduate Fortnight at the Academy of Medicine of New York, 1932.

6. Scott, G. H., and Horning, E. S.: *Am. J. Path.* **8**:329, 1932. Scott, G. H.: *Science* **76**:148, 1932.

appear uniform both to palpation and to unaided vision will often show on examination under ultraviolet radiation a variegated appearance, presenting several distinct colors. Thus small nodules, ordinarily invisible, become apparent.

The results of our examinations, covering many tissues and organs, can be briefly summarized. In regard to the intestinal tract, we find that fluorescence of the serosa varies from purple to deep brown, depending on the amounts of blood and of exudate; the submucosa and muscularis (depending probably on their cellularity) fluoresce various shades of purple and white. A cellular tumor that has extended into the muscular layer of the stomach or rectum will fluoresce from a purple to a deep brown, against the white background of the fibrotic muscular coat. Collections of cholesterol in the wall of an inflamed gallbladder appear golden yellow, even if they are not readily perceptible in natural light.

Similarly, the genital organs will fluoresce from purple to brown, depending on the type of tissue; a soft myomatous nodule of the uterus, containing almost imperceptible hyalinized foci, fluoresces brown with blue-white spots. The ovary often shows cysts which in natural light are not to be identified, but their luteal origin is revealed by the yellow fluorescence. The breast, like other organs, normally fluoresces white, brown or purple, depending on its constituent tissues. A medullary carcinoma in a zone of fibrous tissue appears purple against white. In many instances metastatic foci in lymph glands fluoresce the same color as that of the primary growth. The thyroid fluoresces various shades of brown, depending on the amount of colloid and on the vascularity.

Of the large number of specimens examined, two are described in some detail to show the usefulness of examining tissue with ultraviolet radiation. The first specimen was a breast with a carcinoma. In figure 1 *A*, the tumor is uniformly white, and it is surrounded by contiguous fatty tissues. Under filtered ultraviolet radiation, the area of the tumor, as observed in figure 1 *B*, is definitely divided into two portions. The upper is hazy blue and the lower, white. Below this white region there is a zone containing numerous blue areas. Microscopically, the upper portion is medullary adenocarcinoma, while the lower portion is quite scirrhous. The smaller blue areas are foci of carcinoma metastases. Gross infiltration of the skin by carcinoma is also observed in figure 1 *B*. In another breast, a small tumor nodule in the fat, which in natural light looked much like ordinary fat, was distinctly outlined as a bluish-purple nodule under the radiation.

The second specimen (fig. 2 *A*) was from the upper part of a femur affected by Paget's disease. Under radiation, as observed in figure 2 *B*, the white area extending from the diaphysis into the neck represents the



Fig. 1 A.—Adenocarcinoma of the breast



Fig. 1 B.—Same specimen shown in figure 1 A as seen under filtered ultraviolet radiation.

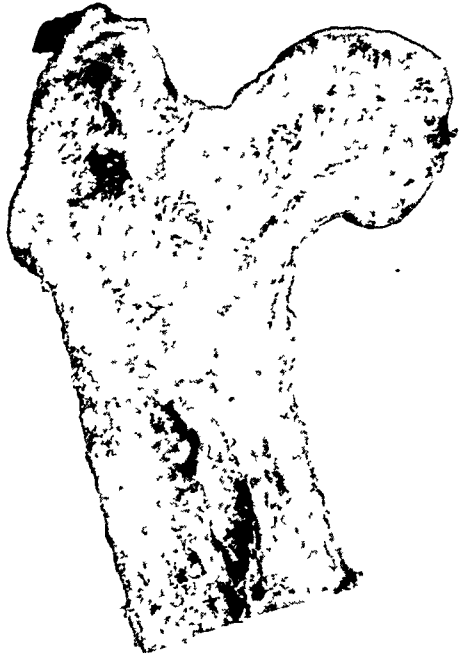


Fig 2 A.—Upper part of a femur (Paget's disease).

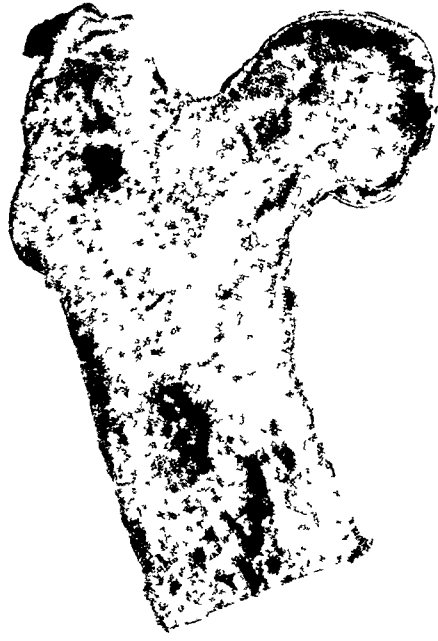


Fig. 2 B.—Same specimen shown in figure 2 A as seen under filtered ultraviolet radiation



most sclerosed and therefore, histologically, the most compact bone. The less sclerosed bone is blue. This was composed of areas showing the mosaic and separated by soft tissue spaces. The most superficial bone, brown-blue in color, was the most newly formed and contained the least calcium. This specimen illustrates unusually well the deposition of periosteal bone in Paget's disease. The large blue osteophytes are due to proliferation and formation of new bone.

CONCLUSION

Filtered ultraviolet radiation aids the surgeon and the pathologist in detecting small areas of disease. These may be imperceptible to the naked eye. It makes possible a gross examination in colors without the use of stains for selective differentiation. As the fluorescence probably depends on the chemical constituents in the nuclei, cytoplasm and intercellular substance of the tissues, we have been unable to find a specific correlation between the fluorescent reaction and the pathologic diagnosis. Nevertheless, the method resolves the tissue into its constituent elements by adding another "color octave" to our range of vision.

NORMAL VARIABILITY IN WEIGHT OF THE ADULT HUMAN LIVER AND SPLEEN

EDITH BOYD, M.D.

MINNEAPOLIS

INTRODUCTION

In a study on the disease conditions in which the liver and the spleen are hypertrophied, Barron and Litman¹ assumed that any adult liver weighing 2,200 Gm. or more and any spleen weighing 300 Gm. or more were hypertrophied. They stated: "The basis for this arbitrary choice of figures is the fact that livers and spleens generally become palpable when they reach such proportions." At the time of their study, Dr. Barron realized that in estimating these values they had failed to take into consideration the probable changes with age, the well recognized sex differences or the general effect of disease on organs not involved in the disease process.

Perusal of the anatomic data on the weights of organs clearly indicates that the organs of the female are usually smaller than those of the male, that most organs decrease in weight during senility, that an organ may increase, be stationary or decrease in weight from early adult life to middle age, that the descriptions from different sources of age changes in early adult life for a given organ are frequently contradictory, and that inanition from any cause tends to reduce the weight of most organs.

In 1906, Vierordt² summarized most of the early data. Reviews of the literature and additional data on the weights of organs, including the liver and the spleen, are given by Greenwood,³ Greenwood and Brown,⁴ Bean and Baker,⁵ Bean,⁶ and Pearl and Bacon.⁷ Jackson⁸ summarized the data on the effects of inanition and malnutrition on

From the Institute of Child Welfare and Department of Anatomy, University of Minnesota.

1. Barron, M., and Litman, A. B.: *Arch. Int. Med.* **50**:240, 1932.
2. Vierordt, H.: *Anatomische, physiologische und physikalische Daten und Tabellen*, ed. 3, Jena, Gustav Fischer, 1906.
3. Greenwood, M., Jr.: *Biometrika* **3**:63, 1904.
4. Greenwood, M., Jr., and Brown, J. W.: *Biometrika* **9**:473, 1913.
5. Bean, R. B., and Baker, W.: *Am. J. Phys. Anthropol.* **2**:1 and 167, 1919.
6. Bean, R. B.: *Am. J. Phys. Anthropol.* **9**:293, 1926.
7. Pearl, R., and Bacon, A. L.: *Johns Hopkins Hosp. Rep.* **21**:297, 1924.
8. Jackson, C. M.: *The Effects of Inanition and Malnutrition Upon Growth and Structure*, Philadelphia, P. Blakiston's Son & Co., 1925; *Arch. Path.* **7**: 1042, 1929; **8**:81 and 273, 1929.

all organs. In his careful review, he stated that most of the data indicate that with inanition there is a marked decrease in the weight of the liver of both man and animals, which tends to be relatively greater than the loss in total body weight. In extreme emaciation the spleen is greatly reduced in weight, the relative loss being twice as great as that of the total body weight, but in early stages of inanition the reduction is slight and difficult to establish because of the great normal variability of the weight of the spleen.

Practically, in the general run of necropsies on adults, the pathologists would probably recognize the reduction in the size of the organ due to old age and hence exclude senile organs from their estimates of normal weight, but they would constantly accept as normal the organs reduced in weight by inanition, thus underestimating both the mean value and the upper limit of normal variation in weight. This source of error is inherent in most pathologic data, since most people are ill for some time before death. Pearl and Bacon⁷ discussed this serious limitation of hospital records of necropsies and stated that the ideal subjects for establishing normal standards would be those killed by violent accidents. Since the staff of the department of pathology of the University of Minnesota perform all coroner's autopsies in Hennepin County, which, according to Bell,⁹ amount to about 200 a year, the records of the department contain considerable data on the weights of organs from persons killed by violent accidents.

In view of these various considerations, at Dr. Barron's request,¹⁰ I undertook to establish more exactly from these data on accidental deaths the probable upper limit of normal weight of the liver and the spleen, including the age and sex differences and, as a necessary step, the normal variability in weight of the liver and the spleen. Dr. Bell granted the free use of all the records of the department of pathology.

CHARACTER AND SELECTION OF DATA

Of the 9,886 necropsies performed on adults 20 or more years of age from January, 1920, to July, 1931, inclusive, death was due to accidental causes, such as fractured skulls, gunshot wounds, suffocations and poisonings in 1,791, or 18 per cent of the subjects. Records of 175 necropsies were not usable because of incomplete information as to age, body length or weight of the liver and spleen. In addition, 34 records for persons 80 years or more of age were omitted because they were too few for statistical analysis. Of the remaining 1,582 subjects, 1,266 were males and 316 females. Information as to race

9. Bell, E. T.: *J. A. M. A.* **90**:896, 1928.

10. Financial aid for this study was given by a grant made to Dr. Barron of the department of medicine by the Research Fund of the Graduate School of the University of Minnesota.

or nationality was given consistently only when the race could be recognized by pigmentation. According to this criterion, the subjects were predominantly Caucasians, since there were only 31 Negroes and 4 Chinese.

The routine procedure in performing a necropsy is first to open the abdomen and inspect its contents, and then to open the thorax and inspect its contents; next the thoracic organs are removed, and finally, the abdominal organs. Usually the spleen is removed before the liver. If an assistant is present, which is generally the case at coroner's necropsies, the organs are weighed immediately after removal; otherwise they are put aside until the end of the examination, when all organs are weighed. When the autopsy is done at the city morgue, the organs are weighed accurately to 1 Gm. on a counterbalance pan scale. When the examination is conducted in an undertaking establishment, hospital morgue or home, the spleen is weighed on a portable spring balance scale reading to 10 Gm. and the liver is weighed on one reading to 25 Gm. With use the spring stretches, so that the scales tend to read too high. More than 95 per cent of the postmortem examinations are made at the city morgue.

In cases of deaths from accidents, the interval between the time of injury and of death may vary from a few minutes to several weeks. If this period is prolonged, more or less malnutrition usually occurs, which, according to Jackson's summary,⁸ reduces the size of the organs, and secondary infections set in, which may either indirectly reduce the weight of the organs by affecting nutrition or directly enlarge the organs by cloudy swelling. To avoid including the weights of organs materially affected either by malnutrition or by secondary infections, I arbitrarily divided the data into two major groups, namely, for persons (I) ill less than twenty-four hours, and (II) ill one day or more. This time limit, first used by Hammar,¹¹ is the same that I used in a similar analysis of the weight of the thymus,¹² in which the weights were significantly lowered when the subjects had died within from one to seven days after the onset of the illness. Since the thymus is probably more sensitive to inanition than any other organ,⁸ this time limit may be assumed to be adequate for eliminating organs which have been affected by inanition and is probably short enough to avoid any marked effects of secondary infections.

While most of the persons killed by accidents were able to work up to the time of injury, some of them were known to be sick or had a

11. Hammar, J. A.: *Arch. f. Anat. u. Entwcklungsgesch.*, supp., 1906, p. 91; *Ztschr. f. mikr.-anat. Forsch.*, vol. 6, 1926; supp., vol. 16, 1929.

12. Boyd, E.: *Am. J. Dis. Child.* **43**:1162, 1932

latent disease process, which was found at necropsy. As a result, two secondary categories were set up: (*A*) no additional disease, and (*B*) additional disease, as indicated by signs or symptoms of disease present before injury or by evidence of disease found post mortem. When infectious processes were apparently secondary to injury, they were classified as (*A*) no additional disease. Signs of old healed infections, such as pleural adhesions, were not considered disease processes. Also, since arteriosclerosis was found in many subjects over 50 years of age, it was accepted as part of the normal age changes in the body. These two decisions were made after plotting all weights of both organs against age and indicating which ones came from subjects with arteriosclerosis or old healed infections. As judged by inspection of the scatter diagrams, these conditions did not affect the weights of either organ.

Many of the protocols contained the diagnosis of alcoholism, and 98 subjects died of acute alcoholism. Unfortunately, the absence of a statement concerning alcohol does not mean that it was not used, and, on the other hand, the diagnosis of alcoholism gives no index of the amount of alcohol consumed. After graphic analysis of the data, I came to the following conclusions:

When the diagnosis was acute alcoholism and there was no fatty degeneration of the liver, the case might be considered one of acute poisoning. When alcoholism was recorded in a death from an accident and the liver showed no fatty degeneration, the case was considered as a death from accident, i. e., (*A*) no additional disease. Finally, when either chronic alcoholism or a fatty liver was present, the case was considered one of (*B*) additional disease. As a matter of fact, when chronic alcoholism was diagnosed, fatty degeneration of the liver was almost always present.

The character of the agent causing death might materially affect the weights of both the liver and the spleen. Poisons which act directly on the central nervous system, such as strychnine, hydrocyanic acid and morphine, would not be expected to change the weight of either organ materially, while those which act by injuring the parenchymatous organs, such as compounds of mercury, arsenic and bismuth, and the strong acids or caustics, such as phenol, lye and compound solution of cresol, would probably materially affect the weights of the liver and the spleen. Hence the cases of poisonings were separated into these two general groups, and burns were arbitrarily added to the latter group.

When a person is killed by violence, excessive loss of blood frequently occurs and is often the cause of death. Preliminary tests indicated that this loss of blood materially reduced the weights of both the

liver and the spleen.¹³ The diagnosis of gross hemorrhage was made when the protocol contained such findings as rupture of the liver, spleen, heart, large blood vessels, hemoperitoneum and hemothorax.

Finally, all organs, and especially the spleen, are apt to be congested in subjects killed by electrocution, suffocation or drownings and carbon monoxide poisoning. This congestion was assumed to be within physiologic limits of the organs.

As a result of these considerations, the data within the two categories, (I) ill less than twenty-four hours and (II) ill one day or more, and their subdivisions, (*A*) no additional disease and (*B*) additional disease, were each again subdivided into (1) all accidents without gross hemorrhage, consisting of (*a*) trauma without gross hemorrhage, (*b*) electrocutions, suffocations and drownings, (*c*) poisoning by carbon monoxide, cyanide compounds, alkaloids and narcotics and (*d*) poisoning by alcohol, (2) trauma with gross hemorrhage and (3) poisonings by heavy metals, strong acids and caustics, and burns, as shown in table 1.

The 312 cases falling under the headings (I) ill less than twenty-four hours, (*A*) no additional disease, (1) accidents without gross hemorrhage, may be considered essentially normal subjects; hence a reasonable sample from which to establish standards of normal variability in weights of organs. The 489 cases falling under the headings (I) ill less than twenty-four hours, (*A*) no additional disease, (2) trauma with gross hemorrhage are equally normal subjects. They are comparable to the laboratory animal killed by a blow on the head and then bled by cutting the vessels of the neck, while the group I have considered normal is comparable in part, at least, to the laboratory animal killed by etherization.

13. The marked effect of gross hemorrhage on these weights was found inadvertently. In the first sorting of the record cards, I had separated those cases with rupture of either the liver or the spleen, with the idea of excluding them from the normal data. Graphic analysis showed that the weights of these ruptured organs fell within the same range as the organs from other cases of trauma, but large numbers of them were in the lower part of the range. Also, if only the livers were ruptured, the nonruptured spleens from the same subjects tended to fall in the same part of the ranges as the weights of the ruptured spleens. The same relation held for the weights of ruptured spleens and nonruptured livers. When the traumatic cases without rupture of either liver or spleen were divided into those with and those without gross hemorrhage from other ruptured organs, the weights from cases without any gross hemorrhage tended to fall above the weights from those with hemorrhage. Moreover, the weights from cases of hemorrhage did not seem to vary according to source of hemorrhage, i. e., the livers and spleens themselves or other organs. Hence it was concluded that massive hemorrhage from any part of the body reduced the weight of the liver and spleen as much as hemorrhage from the organs themselves.

After discussing this problem with me, Dr. Charlotte Van Winkle¹⁴ carried out a comparison of both the weights of the liver and the spleen between guinea-pigs killed by a blow on the head and those killed by etherization. Her findings, which will be published elsewhere, show that the liver is significantly smaller in the group that was bled, while there is no demonstrable difference between the weights of the spleen in this group bled and the group that was killed by etherization. The latter finding is not in agreement with the findings for man, in whom both organs are reduced by gross hemorrhage, as will be demonstrated later. A possible physiologic explanation is that the spleen contracts in the struggling etherized animal, thus emptying the spleen of blood as effectively as by bleeding by cutting the large vessels while the heart

TABLE 1.—*Case Incidence According to Type of Accident Causing Death, Duration of Illness, Presence or Absence of Disease and Sex*

	I. Ill Less Than 24 Hours (1,074 Cases)						II. Ill 1 Day or More (508 Cases)						Totals
	A. No Additional Disease			B. Additional Disease			A. No Additional Disease			B. Additional Disease			
	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	
(1) All accidents without gross hemorrhage	239	73	312	121	41	162	145	30	175	149	38	187	836
(2) Trauma with gross hemorrhage	406	83	489	58	12	70	79	13	92	27	7	34	685
(3) Poisonings by heavy metals, burns, etc.	18	5	23	12	6	18	9	5	14	3	3	6	61
Totals	663	161	824	191	59	250	233	48	281	179	48	227	1,582

is still beating. Further consideration of this problem will be taken up by Dr. Van Winkle in her article.

Since most deaths from disease are not associated with gross hemorrhage, the nonhemorrhagic group has been used for establishing normal standards of variability in the weight of the liver and spleen.

ANALYSIS OF DATA

When the weights of the liver and spleen from the nonhemorrhagic group just selected as normal are plotted for both sexes against age (charts 1 and 2), the weights of the liver in both sexes seem to increase slightly from 20 to 50 years of age, especially in the upper range of weight, then to decrease, and the livers of the males tend to be larger than those of the females. On the other hand, the weights of the spleen in both sexes appear to decrease both in amount and variability from 20 to 50

14. Pathologist and Director of Laboratory, Glen Lake Sanatorium, Oak Terrace, Minn.

years, and the weights of the spleen in the females do not appear to be materially smaller than those of the males.

The central trend in weight of these organs could be represented by various methods. The most common procedure in current use is to average the weights for given age periods, then to pass a trend line through these averages by a point to point line drawn in from average

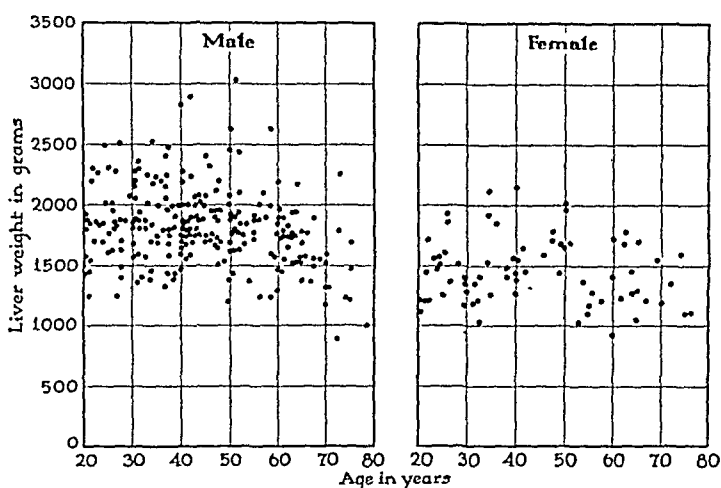


Chart 1.—Scatter diagrams of the weights of the livers with age from normal males and females, i. e., those in the group (I) ill less than twenty-four hours, (A) no additional disease, (1) all accidents without gross hemorrhage.

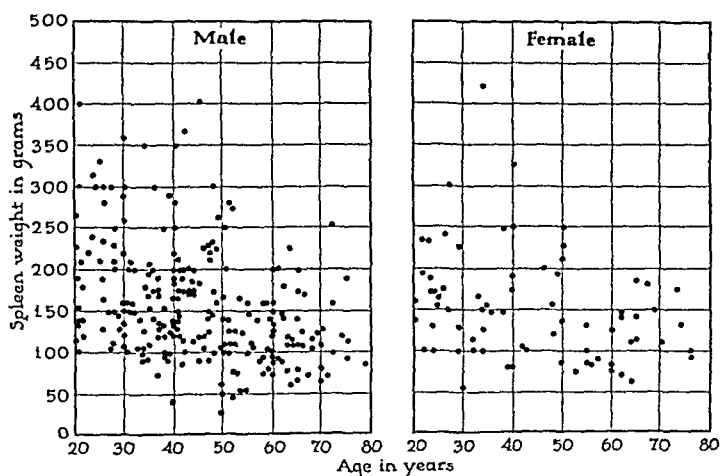


Chart 2.—Scatter diagrams of the weights of the spleen with age from normal males and females, i. e., those in the group (I) ill less than twenty-four hours, (A) no additional disease, (1) all accidents without gross hemorrhage.

to average, or by a smooth curve drawn by inspection to the averages, or by fitting a line to the averages by the method of least squares, or, for the weights of the spleen which appear to have approximately a straight line trend with age, by fitting the regression line by the Pearsonian correlation technic. The variability around these trends could be measured in terms of one and two standard deviations from the

mean weights for each age period or from the regression line for all age periods, so that the middle two thirds of the weights would fall between plus and minus one standard deviation and the middle 95 per cent of the weights between plus and minus two standard deviations. Actually, these methods were first applied to these data, but it was found that the weights of both organs, and especially those of the spleen, like those of the thymus,¹² were so skew that the lower two standard deviations line fell below all the weights, instead of 2.5 per cent of the weights falling below it.¹⁵

Construction of Standards of Normal Variability in the Weight of the Liver and the Spleen.—As a result of these findings, as in the analysis of the weights of the thymus, the medium weights,¹⁶ or 50 percentiles of weight for 10 year age periods, were used to represent the central trend; the weight range from the 25 to the 50 percentiles, the middle 50 per cent of the weights, and the weight range from the 10 to the 90 percentiles, the middle 80 per cent of the weights. To these were added the 2.5 and the 97.5 percentiles as the probable lower and upper limits of normal variability.¹⁷

The designated percentiles were found for the weights of both organs in each 10 year age group for both sexes by the graphic method given by Yule.¹⁸ The values for each percentile along with the minimum and maximum weights for the liver are given in table 2, and for the spleen in table 3. Whenever there were marked irregularities from age period to age period, the values were smoothed by one application of three point smoothing.¹⁹

15. When the weights were plotted on a six-zone standard based on plus and minus one and two standard deviations, the Chi-square and *P* for the difference between the observed and theoretical number in each zone were 14.79 and 0.01 for the liver and 27.21 and 0.000057 for the spleen.

16. On the average, in these data the median weight of the liver is in males 24 Gm., or 1.4 per cent below the mean weight, and in females 48 Gm., or 3.3 per cent. The median weight of the spleen is on the average in males 13 Gm., or 8.3 per cent below the mean weight, and in females 10 Gm., or 6.8 per cent. The means, standard deviations and correlations of liver and spleen, liver and height and spleen and height will be published in a subsequent report.

17. These arbitrary limits were chosen because they represent essentially the same level of probability, i. e., 0.025, commonly used as the dividing line between probably significant and nonsignificant deviations within a normal distribution. Hence, the 97.5 and 2.5 percentile lines of these skew distributions correspond approximately to plus and minus three probable errors, or two standard deviations from the mean of normal distributions.

18. Yule, G. U.: *An Introduction to the Theory of Statistics*, ed. 9, London, Charles Griffin & Co., 1929.

19. The weight for the calculated 2.5 percentile can be less than the observed minimum weight when there are few weights and several are near the minimum weight, so that the curve drawn in by inspection extends beyond the minimum weight. The same principle applies when the weight for the 97.5 percentile is larger than the observed maximum weight.

Graphic charts giving the variability for the total age period for each organ and sex were constructed by plotting the weights for the 97.5, 90, 75, 50, 25, 10 and 2.5 percentiles of each 10 year age interval against the mid-age of the interval and by joining all 97.5 percentiles with a continuous line, all 90 percentiles with another continuous line, and so on for the 75, 50, 25, 10 and 2.5 percentiles, respectively.

TABLE 2.—*Percentiles of Weight for the Normal Liver*¹⁹

Age Interval, Years	Num- ber of Cases	Maxi- mum Weight, Gm.	Percentiles of Weight in Grams							Mini- mum Weight, Gm.
			97.5	90	75	50	25	10	2.5	
			Males							
20 to 29	38	2,500	2,480	2,300	2,000	1,820	1,640	1,420	1,300	1,235
30 to 39	54	2,515	2,520	2,310	2,030	1,830	1,670	1,490	1,370	1,327
40 to 49	58	2,900	2,600	2,290	2,030	1,840	1,670	1,510	1,350	1,470
50 to 59	39	3,020	2,570	2,190	2,000	1,840	1,640	1,510	1,350	1,200
60 to 69	37	2,400	2,420	2,070	1,890	1,740	1,580	1,420	1,320	1,300
70 to 79	13	2,263	2,140	1,860	1,640	1,380	1,180	1,020	900	900
Females										
20 to 29	19	1,920	1,900	1,720	1,560	1,440	1,280	1,140	1,080	1,114
30 to 39	14	2,120	2,040	1,820	1,620	1,460	1,320	1,200	1,080	1,023
40 to 49	11	2,130	2,100	1,910	1,690	1,440	1,290	1,180	1,220	1,250
50 to 59	11	2,000	1,990	1,870	1,700	1,430	1,260	1,140	1,010	1,020
60 to 69	13	1,780	1,880	1,780	1,590	1,380	1,150	1,050	910	925
70 to 79	5	1,595	1,760	1,600	1,380	1,180	1,100	1,040	1,000	1,100

TABLE 3.—*Percentiles of Weight for the Normal Spleen*¹⁹

Age Interval, Years	Num- ber of Cases	Maxi- mum Weight, Gm.	Percentiles of Weight in Grams							Mini- mum Weight, Gm.
			97.5	90	75	50	25	10	2.5	
			Males							
20 to 29	38	400	364	318	250	194	144	116	96	90
30 to 39	54	360	356	281	220	172	131	106	86	75
40 to 49	58	400	327	234	187	144	112	86	65	75
50 to 59	39	280	285	229	172	135	108	84	61	25
60 to 69	37	225	243	205	147	113	94	74	61	60
70 to 79	13	255	234	188	136	108	90	74	66	65
Females										
20 to 29	19	500	360	255	205	165	130	95	65	65
30 to 39	14	420	310	258	200	162	118	85	63	55
40 to 49	11	325	293	252	195	142	102	80	65	80
50 to 59	11	250	273	227	182	135	95	77	67	75
60 to 69	13	284	230	198	160	113	87	78	68	61
70 to 79	5	175	195	175	140	110	95	78	70	90

The results are shown in charts 3 and 4, and the scatter of observed values against the standards constructed from them in charts 5 and 6. According to the construction of the graphs, 2.5 per cent of the weights of normal organs would be expected to fall both above the 97.5 percentile line and below the 2.5 percentile line, 7.5 per cent in the clear zones between the 97.5 and 90 and the 10 and 2.5 percentile lines, 15 per cent in the lightly shaded zones between the 90 and 75 and the 25 and 10 percentile lines, and 25 per cent in the heavily shaded zones between both the 75 and 50 and the 50 and 25 percentile lines.

According to these charts and tables, the liver of the male tends to increase from a median weight of 1,820 Gm. at 25 years to a median weight of 1,840 Gm. at 55 years and then to decrease 360 Gm., or 20 per cent, to a median weight of 1,480 Gm. by 75 years. The median

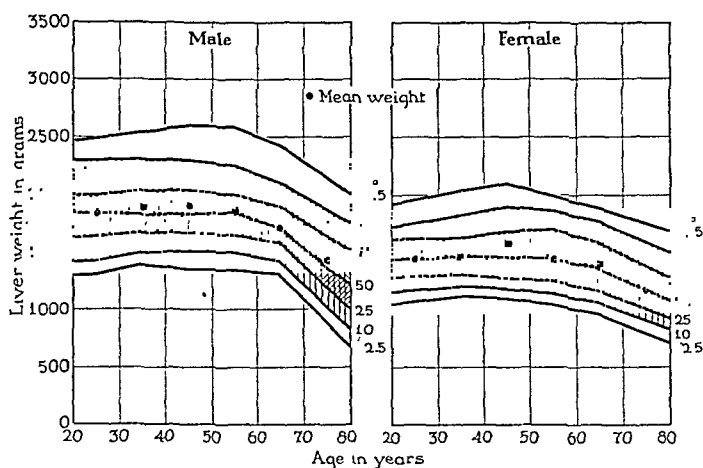


Chart 3.—Graphic standards of normal variability in weight of the liver of both the male and the female based on the data in chart 1. The percentage figures given at the side of each panel indicate the percentiles of weight. Fifty per cent of normal weights may be expected to fall in the heavily shaded zone, 80 per cent in the totally shaded zone and 95 per cent in the total zone limited by the 97.5 and the 2.5 percentile lines. For practical purposes, the last two percentile lines may be considered the usual upper and lower limits of normal variability in weight of the liver.

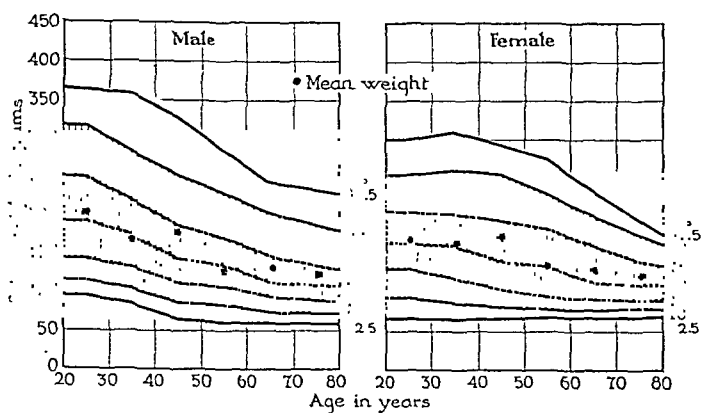


Chart 4.—Graphic standards of normal variability in weight of the spleen of both the male and female based on the data in chart 2. The percentage figures given at the side of each panel indicate the percentiles of weight. Fifty per cent of normal weights will be expected to fall in the heavily shaded zone, 80 per cent in the totally shaded zone and 95 per cent in the total zone limited by the 97.5 and the 2.5 percentile lines. For practical purposes, the last two percentile lines may be considered the usual upper and lower limits of normal variability in the weight of the spleen.

weight of the liver of the female fluctuates between 1,460 and 1,430 Gm. in the four decades from 20 to 60 years, then definitely decreases approximately 250 Gm., or 11 per cent, to 1,180 Gm. by 75 years. Thus, the liver of the male is from 200 to 400 Gm. heavier than the liver of the female, and the liver in both sexes is essentially stationary in weight from 20 to 55 years of age and then decreases in weight.

The variability in the weight of the liver, as illustrated by the various shaded zones, shows that on the average the middle 50 per cent of weights covers a range of 370 Gm. in the male and 360 Gm. in the female, the middle 80 per cent a range of 840 Gm. in the male and 660 Gm. in the female, and the middle 95 per cent a range of 1,190 Gm. in the male and 900 Gm. in the female. In relative terms, the 75 percentile line averages 15 per cent above the median line for males and

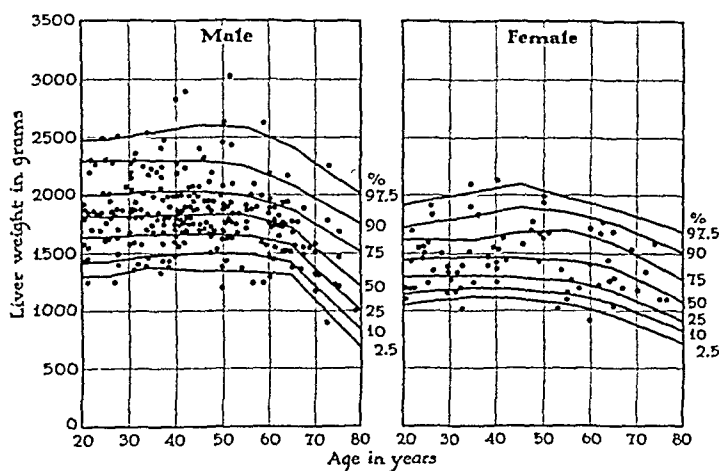


Chart 5.—Graph showing the weights of the liver from normal males and females, chart 1, plotted on the percentile standard, chart 3, constructed from these weights.

11 per cent for females, while the 25 percentile line averages 10 per cent below the median line for both sexes. The 97.5 percentile line averages 42 and 40 per cent above the median line, and the 2.5 percentile line 26 and 24 per cent below it. These findings show the marked skewness of the weights in both sexes and for all age periods.

In contrast to the liver, the spleen in both sexes tends to decrease throughout adult life. The median weight of the spleen of the male decreases 86 Gm., or 44 per cent, from 194 Gm. at 25 years to 108 Gm. at 75 years, and that of the female decreases 55 Gm., or 33 per cent, from 165 Gm. at 25 years to 110 Gm. at 75 years. There is no material difference between the median weights for the two sexes, except in the decade from 20 to 30 years, when the spleen of the male is 14 per cent heavier than that of the female. In the male the middle 50 per cent of

weights cover a mean range of 72 Gm., the middle 80 per cent a mean range of 156 Gm. and the middle 95 per cent a mean range of 227 Gm. In the female these ranges are 76 Gm., 146 Gm. and 156 Gm., respectively. Relatively, this variability is about twice that of the liver. In the male the 75 percentile line averages 28 per cent above the median weight, and the 25 percentile line averages 23 per cent below it; the 97.5 percentile line averages 111 per cent above the median weight and the 2.5 percentile line averages 49 per cent below. In the female the 75 and 25 percentile lines average 31 and 23 per cent above and below the median weight, respectively, and the 97.5 and 2.5 percentile lines average 94 and 47 per cent above and below it.

This great normal variability in the spleen, as estimated from these data, is probably due to the normal contractility of the organ. In data

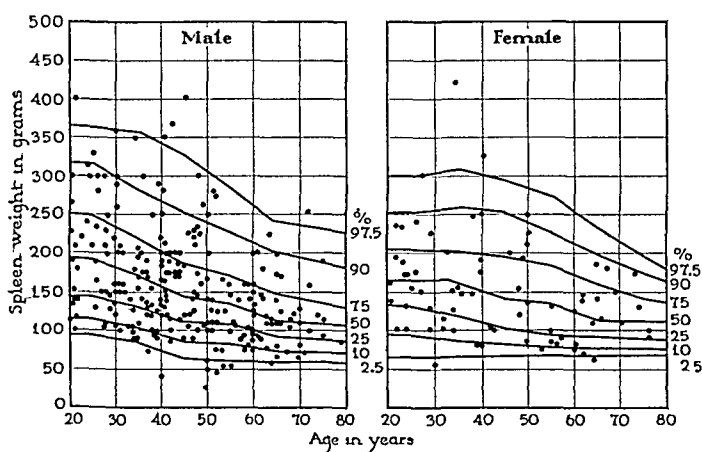


Chart 6.—Graph showing the weights of the spleen from normal males and females, chart 2, plotted on the percentile standard, chart 4, constructed from these weights.

from man, the state of contraction or dilatation cannot be controlled. As a result, the weights of the spleen from conditions known to cause contraction would tend to fall in the lower zones, and those from conditions which cause dilatation would tend to fall in disproportionate numbers in the upper zones of these standards. The latter possibility apparently occurred in the cases of poisoning from carbon monoxide, cyanide and other poisons, since 70 per cent of the weights in this group fell above the median line and only 30 per cent below it, in contrast to the expected 50 per cent on each side of the line.

That this disproportion is more than would be expected to occur by chance alone is demonstrated in the following test of the standard:

The goodness of the fits of the standards to the weights of both the liver and the spleen in the normal group, (I) ill less than twenty-four hours, (A) no additional disease, (1) all accidents without gross hem-

orrhage, and its subdivisions was tested by the Chi-square method. (The steps of this method are illustrated in table 6 for the comparison of the hemorrhagic group with the standard.) The fits for the total and all subgroups, except the weights of the spleen in cases of non-alcoholic poisoning, were found to be excellent, since the probability integrals, P , given in tables 4 and 5 were usually close to 0.90 and never less than 0.22, indicating that the differences could occur from chance alone from twenty-two to ninety times in a hundred.

Commonly, if P is 0.01 or less, i. e., chance could account for such a difference only once in a hundred times, it is assumed that the difference in that given comparison is not due to chance, and this difference is called significant. Hence, since P for the subgroup, poisonings by carbon monoxide, cyanide and other poisons, is 0.003, the 70 per cent of weights of the spleen above the median is significantly above the expected 50 per cent. Pathologists have the impression that relatively large spleens are found in cases of carbon monoxide poisoning. Because of this, I separated on the graphs the weights in cases of poisoning due to carbon monoxide from those due to other poisons. Both groups, however, tend to have a relatively high number of weights in the upper range of the normal variability. Hence, in the persons killed by the poisons which act on the central nervous system, the spleen tends to be larger than in persons killed by trauma. The liver of these same subjects shows no such tendency. Possibly, along with the paralysis of either respiratory or cardiac centers in the central nervous system, the vasomotor control of vessels to the spleen is stopped so that the spleen becomes dilated and filled with blood. On the other hand, in the various types of trauma, death has taken place with the spleen in any phase of its possible physiologic range from marked contraction to extreme dilatation.

On the whole, these standards may be assumed to be reasonable estimates of the central trend of the weights of the liver and the spleen with age and the variability around that central trend. The standard for males is more reliable for both organs than that for females, because the basic sample consisted of four times as many cases. Also the standards for the liver are more reliable than those for the spleen, because of the great physiologic variability of the spleen. The 97.5 and 2.5 percentile lines may be assumed to represent the probable limits of normal size, although two or three weights in every hundred in this series fell above and below these lines, and the same number would be expected in another identical series. However, the likelihood is great that the extreme upper and lower weights in this series actually came from subjects with some pathologic condition which was not recognized at postmortem examination or which did not leave adequate signs to be recognized by the customary methods of making the examinations.

TABLE 4.—Comparison of the Weights of the Liver in the Various Subdivisions of the Normal Group (1) Ill Less Than Twenty-Four Hours, (A) No Additional Disease, (1) All Accidents Without Gross Hemorrhage, With the Normal Standard

	Percentage of Weights										Percentage of Weights	
	Sex	Number of Weights	Between the Percentile Lines								χ ²	P
			Above 97.5 Line	97.5 to 90	90 to 75	75 to 50	50 to 25	25 to 10	10 to 2.5	Below 2.5 Line		
Percentage of weights expected.....			2.5	7.5	15	25	25	15	7.5	2.5	n'	
(1) All accidents without gross hemorrhage.....	Male.....	239	3	6	16	26	24	16	6	3	6	0.56
	Female.....	73	3	10	12	23	29	12	7	4	4	0.59
	Both sexes..	312	3	6	15	26	25	15	6	4	6	0.08
(a) Trauma without gross hemorrhage.....	Male.....	102	4	1	15	27	20	17	12	4	6	7.18
	Female.....	44	5	11	13	23	23	11	9	5	4	0.55
	Both sexes..	146	4	4	15	26	21	15	11	4	6	5.14
(b) Electrocutions, suffocations and drownings	Both sexes..	45	4	7	20	13	31	20	3	2	4	3.80
(c) Poisoning by carbon monoxide, hydrocyanic acid, etc.	Both sexes..	73	2	7	7	33	32	14	1	4	4	6.17
(d) Poisoning by alcohol.....	Both sexes..	48	0	15	23	25	21	10	4	2	4	4.67

TABLE 5.—Comparison of the Weights of the Spleen in the Various Subdivisions of the Normal Group, (1) Ill Less Than Twenty-Four Hours, (A) No Additional Disease, (1) All Accidents Without Gross Hemorrhage, With the Normal Standard

	Percentage of Weights										Percentage of Weights	
	Sex	Number of Weights	Between the Percentile Lines								χ ²	P
			Above 97.5 Line	97.5 to 90	90 to 75	75 to 50	50 to 25	25 to 10	10 to 2.5	Below 2.5 Line		
Percentage of weights expected.....			2.5	7.5	15	25	25	15	7.5	2.5	n'	
(1) All accidents without gross hemorrhage.....	Male.....	239	2	8	15	26	23	15	8	3	6	0.53
	Female.....	73	6	1	19	22	23	18	8	3	4	0.81
	Both sexes..	312	3	6	16	25	23	16	8	3	6	1.20
(a) Trauma without gross hemorrhage.....	Male.....	102	1	8	13	25	25	18	8	2	6	0.99
	Female.....	44	4	0	16	21	25	18	11	5	4	2.18
	Both sexes..	146	2	5	14	24	25	18	9	3	6	2.28
(b) Electrocutions, suffocations and drownings	Both sexes..	45	2	5	20	20	22	18	2	2	4	3.28
(c) Poisoning by carbon monoxide, hydrocyanic acid, etc.	Both sexes..	73	7	12	22	29	15	10	4	1	4	13.74
(d) Poisoning by alcohol.....	Both sexes..	48	0	2	12	19	29	17	17	4	4	6.17

Every pathologist is familiar with the case in which an obviously ill patient dies but no cause of death can be found. Moreover, in this series the coroner's records are apt to be incomplete concerning symptoms previous to injury.

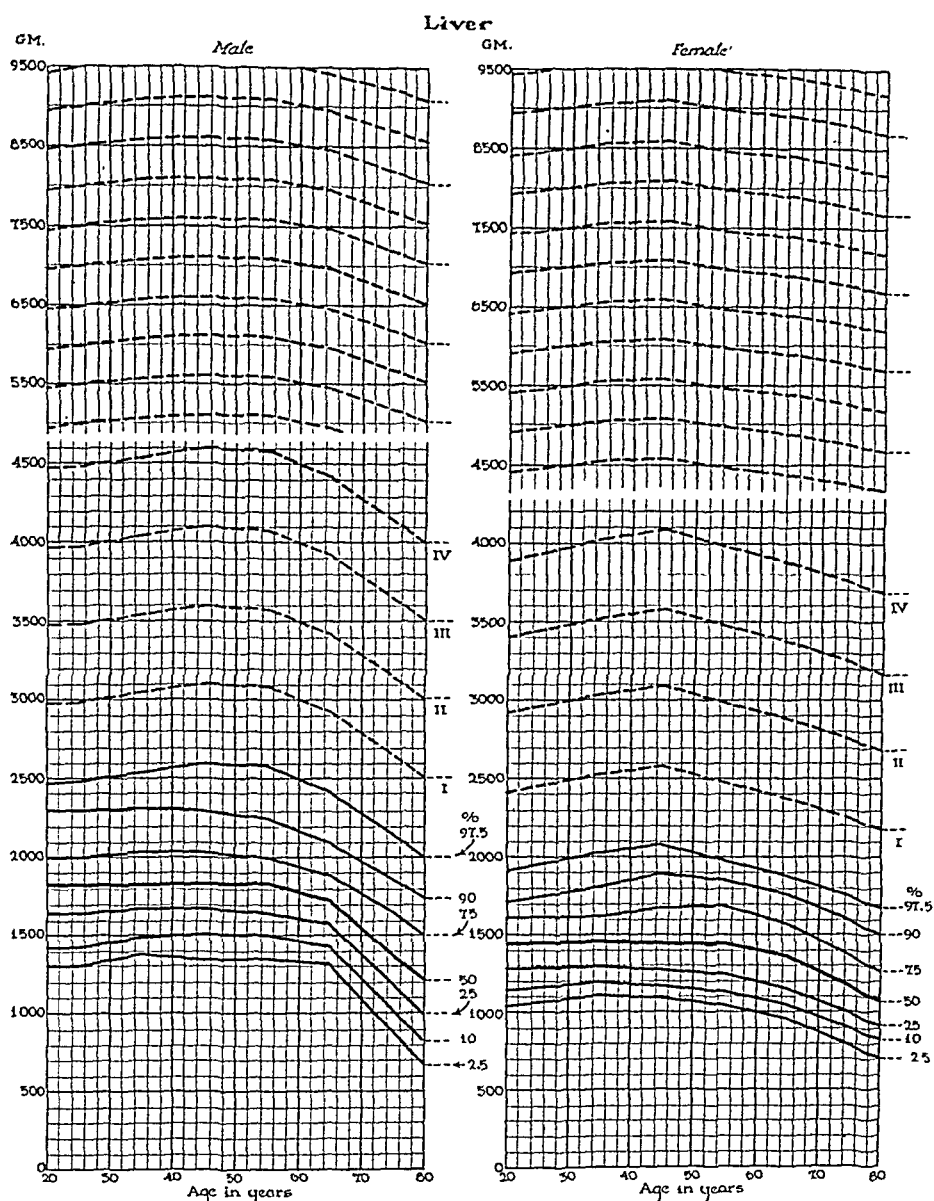


Chart 7.—Work chart of 500 Gm. zones of hypertrophy of the weight of the liver of both the male and the female superimposed above the 97.5 percentile lines of chart 3. Above zone IV the scale was reduced in order to include a sufficient number of zones for pathologic weights.

Zones of Hypertrophy.—In order to make the standards of normal variability useful for Dr. Barron's purposes, namely, degree of hypertrophy of the liver and the spleen in various disease conditions, zones of 500 Gm. for the liver and 100 Gm. for the spleen were drawn in above the 97.5 percentile line, as shown in charts 7 and 8. Inspection

of chart 3 or 7 indicates that the estimate of the upper limit of the normal weight of the liver at 2,200 Gm. made by Barron and Litman¹ would have included approximately from 10 to 15 per cent of the livers of normal males, and especially those of men under 60 years of age,

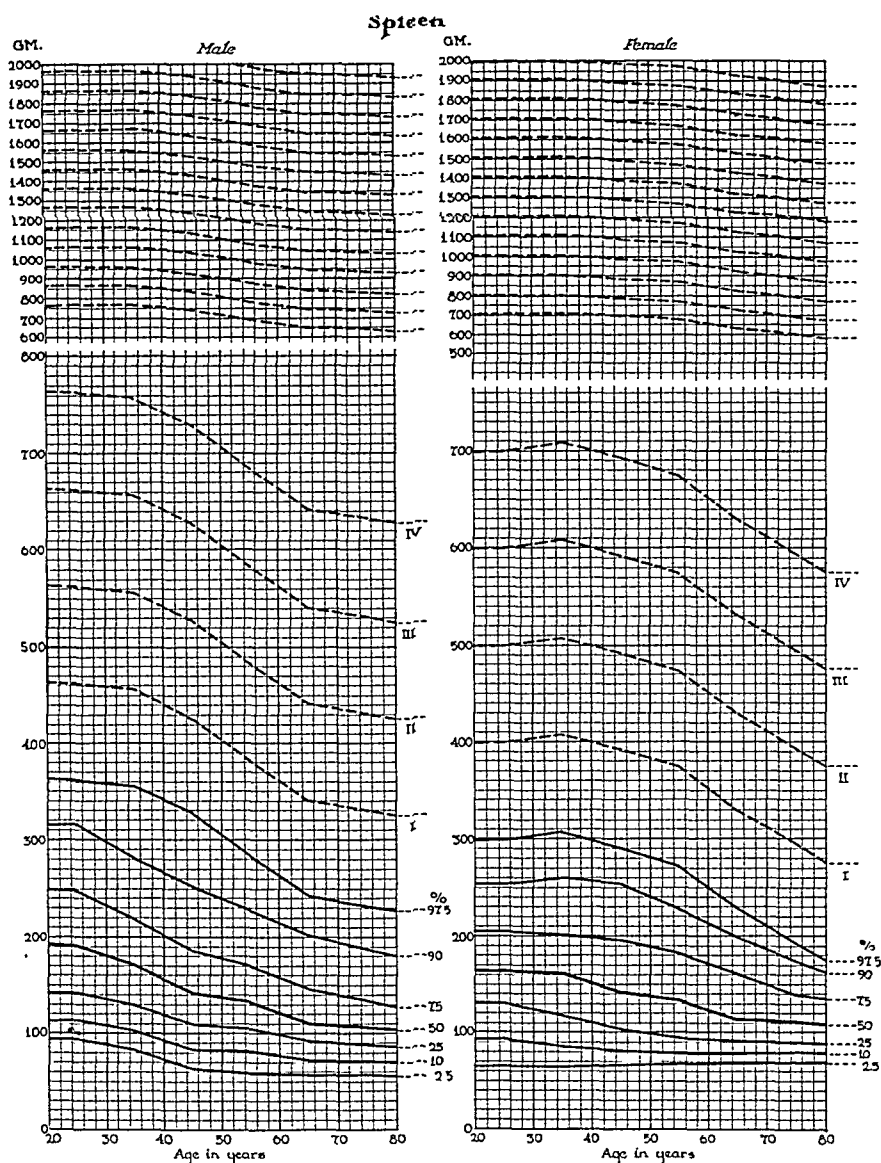


Chart 8.—Work chart of 100 Gm. zones of hypertrophy of the weight of the liver of both the male and the female superimposed above the 97.5 percentile lines of chart 4. Above zone IV the scale was reduced in order to include a sufficient number of zones for pathologic weights.

while certain hypertrophied livers in females would not have been considered enlarged. Inspection of charts 4 and 8 shows that their estimate of 300 Gm. for the upper limit of the normal weight of the spleen would include as hypertrophied about 10 per cent of the spleens in

normal young men and a few of those of young women, while after middle age certain hypertrophied organs would not have been included in their series. This would indicate, on the basis of their assumption that spleens weighing 300 Gm. and livers weighing 2,200 Gm. are palpable, that about 15 per cent of the livers of healthy mature men are palpable and about 10 per cent of the spleens of young men are palpable. This fits with the common clinical practice of accepting, in the absence of symptoms, a just palpable liver or spleen as probably normal. Since they were interested primarily in the very large livers and spleens, weighing 4,000 and 550 Gm., respectively, these findings will not affect their analysis of the importance of hepatomegaly and splenomegaly in differential diagnosis.²⁰

Comparison of the Data for Accidental Deaths, Which Were Not Used in Establishing the Standard, With the Normal Standard.—The effect of gross hemorrhage on the weight of both organs is shown in charts 9 and 10, in which the weights from the hemorrhagic group, (1) ill less than twenty-four hours, (A) no additional disease, (2) trauma with gross hemorrhage, are plotted on the standards. On inspection, a disproportionate number of weights of both organs seems to fall in the lower zones of normal variability, indicating that massive hemorrhage shortly before death materially lowers the weight of both the liver and the spleen. Whether or not this disproportion is due to chance in sampling or to the gross hemorrhage has been tested by Chi-square in the same manner as the standard was tested.

The steps in calculating Chi-square for the weights of the liver in males are illustrated in table 6. The value of P for a given number of zones, n' , and the value of Chi-square obtained may be found in Elderton's tables of Chi-square (Pearson),²¹ in a nomogram given by Dunn²² and in Fisher's tables of Chi-square,²³ when n equals $(n' - 1)$. For weights of livers of the male the Chi-square of 354 is so great that such deviations from the expected number in each zone would not occur by chance once in a million times, since P is less than 0.000000.

20. Dr. Barron will report later on hypertrophy of the liver and spleen as measured by these standards. We hope ultimately to present a compromise by rank correlation of the interrelation between variability of both organs in the same disease conditions.

21. Pearson, Karl: *Tables for Statisticians and Biometricians*, ed. 2, London, The Biometric Laboratory, University College, 1924, pt. 1.

22. Dunn, H. L.: *Physiol. Rev.* 9:275, 1929.

23. Fisher, R. A.: *Statistical Methods for Research Workers*, ed. 3, London, Oliver & Boyd, 1930.

As stated before, in common statistical practice a P of 0.01,²⁴ indicating that chance could cause such a difference only once in a hundred times, is considered adequate evidence of a real difference between two samples. Hence the liver of the female and the spleen of both the male and the female in the hemorrhagic group are also significantly different from the standard, because their P 's are 0.003, 0.000000 and 0.000000, respectively. Since these differences, as illustrated in charts 9 and 10 and

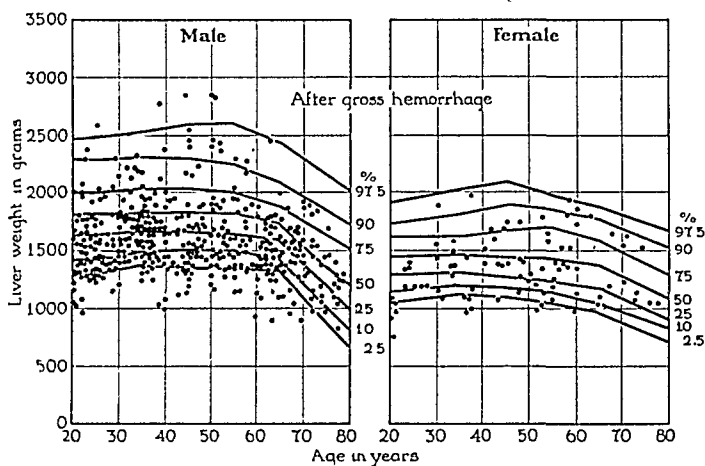


Chart 9.—Graphs showing the weights of the livers from normal males and females dying of trauma with gross hemorrhage plotted on the standards of normal variability of liver weight, chart 3.

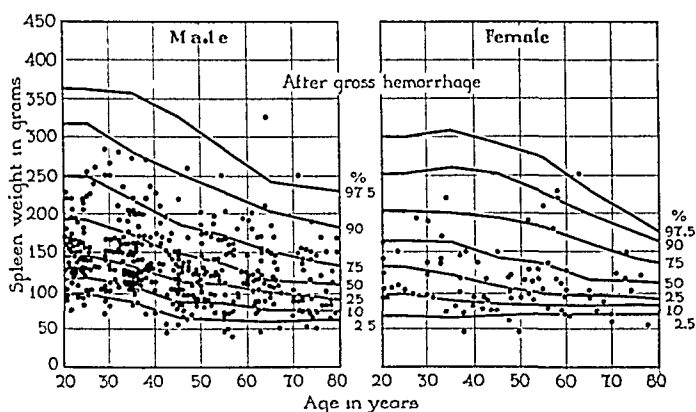


Chart 10.—Graphs showing the weights of the spleen from normal males and females dying of trauma with gross hemorrhage plotted on the standards of normal variability of spleen weight, chart 4.

24. For the convenience of those who do not have the statistical tables at hand, the following table gives the values of Chi-square for a given number of zones, n' , at which P is 0.01:

n'	8	6	4	2
χ^2	18	15	11	9

tables 7 and 8, consist of a general lowering of the weights, the interpretation is made that massive hemorrhage materially lowers the weight of both the liver and the spleen.

In like manner, the weights for the other groups excluded from the normal data for accidental deaths listed in table 1 were compared with the standard and the findings summarized in tables 7 and 8. Since fatty degeneration of the liver causes marked hypertrophy, this group for the liver was separated from the groups in which additional disease was present. Also the number of weights in comparable zones of the standards for the males and the females were combined, because no sex differences in the distribution of the weights on the standard were

TABLE 6.—*The Chi-Square Method of Comparing Observed with Theoretically Expected Number of Weights in Each Zone of the Normal Standard*

	Percentile Zones								Totals
	Above 97.5 Line	97.5 to 90 Line	90 to 75 Line	75 to 50 Line	50 to 25 Line	25 to 10 Line	10 to 2.5 Line	Below 2.5 Line	
Expected percentage of weights	2.5	7.5	15	25	25	15	7.5	2.5	100
Expected number of weights, T	10.15	30.45	60.90	101.50	101.50	60.90	30.45	10.15	406
Observed number of weights, O*	5	14	23	53	82	88	77	59	406
T - O	+5.15	+16.45	+32.90	+48.50	+19.50	-27.10	-46.55	-48.85	0
(T - O) ²	26.52	270.60	1082.41	2352.25	380.25	734.41	2166.00	2386.32	
(T - O) ² /T	2.61	8.89	17.77	23.17	3.75	12.06	71.16	235.11	374.52
$\chi^2 = \text{sum of } (T - O)^2/T = 374.52$ $n' \text{ of Elderton's table of } \chi^2 = \text{number of zones} \approx 8 \therefore P = 0.000000$									

* Example: The hemorrhagic group, (1) ill less than twenty-four hours, (A) no additional disease, (2) trauma with gross hemorrhage, weights of 406 livers from males, shown in the first panel of chart 9.

demonstrable for any disease. Whenever the combining of the numbers of the sexes did not increase the number expected in the end-zones to ten, the zones were combined until at least that many were expected, and then Chi-square was calculated for the resulting reduced number of zones, 6, 4 or 2, as indicated by the values of n' in the tables.²⁴

Study of the tables indicates that when disease was present at time of injury, the variability was usually significantly increased, i. e., a disproportionate number fell in the extreme upper and lower zones, and when illness had lasted more than one day, an increased number of weights of livers fell in the lower ranges, but the weights of spleens showed no significant deviation from the normal. The latter findings are in agreement with Jackson's summary⁸ of the effects of inanition on both the liver and the spleen, namely, that both are reduced, but the reduction of the spleen cannot be demonstrated as early in inanition as

TABLE 7.—Comparison of the Weights of the Liver From the Accidental Deaths, Not Used in Establishing the Standard, With the Normal Standard

	Number of Weights for Both Sexes	Percentage of Weights												χ^2	P	Percentage of Weights	
		Between the Percentile Lines														Above 50 Line	Below 50 Line
		Above 97.5 Line		97.5 to 90		90 to 75		75 to 50		50 to 25		25 to 10					
Percentage of weights expected.....		2.5	7.5	15	25	25	15	7.5	2.5	2.5	7.5	15	25	2.5	7.5	n'	
(1) Accidents Without Gross Hemorrhage																	
(I) Ill less than 24 hours:																	
(A) No additional disease.....	97	9	11	11	23	20	15	5	6	6	11.32	0.05	54	46			
(B) Additional disease.....	65	26	12	28	20	8	4	0	2	4	61.70	0.00	86	14			
(C) Fatty liver.....																	
(II) Ill 1 day or more:																	
(A) No additional disease.....	175	2	6	13	22	22	19	9	7	6	11.95	0.04	43	57			
(B) Additional disease.....	130	9	14	14	14	20	14	10	5	6	32.90	0.00	51	49			
(C) Fatty liver.....	57	25	31	12	14	11	7	0	0	4	57.88	0.00	82	18			
(2) Trauma With Gross Hemorrhage																	
(I) Ill less than 24 hours:																	
(A) No additional disease...	489	1	4	8	13	22	20	17	15	6	302.51	0.00	26	74			
(B) Additional disease.....	47	4	5	4	13	19	19	21	15	4	23.55	0.00	26	74			
(C) Fatty liver.....	23	13	9	17	22	26	0	4	9	2	1.08	0.30	61	39			
(II) Ill 1 day or more:																	
(A) No additional disease.....	92	2	2	12	22	20	17	11	14	6	26.03	0.00	38	62			
(B) Additional disease.....	25	0	0	12	36	8	32	8	4	2	0.04	0.80	48	52			
(C) Fatty liver.....	9	78	22			
(3) Poisoning with Heavy Metals																	
(I) Ill less than 24 hours:																	
(A) No additional disease.....	23	0	4	13	9	26	35	9	4	2	2.13	0.15	26	74			
(B) Additional disease.....	15	0	0	20	13	20	20	13	14	33	67			
(C) Fatty liver.....	3			
(II) Ill 1 day or more:																	
(A) No additional disease.....	14	0	21	22	14	14	22	7	0	57	43			
(B) Additional disease.....	6			

TABLE 8.—Comparison of the Weights of the Spleen From the Accidental Deaths, Not Used in Establishing the Standard, With the Normal Standard

	Number of Weights for Both Sexes	Percentage of Weights										Percentage of Weights				
		Between the Percentile Lines										n'	χ ²	P	Above Below 50 50 Line Line	
		Above 97.5 Line	97.5 to 90	90 to 75	75 to 50	50 to 25	25 to 10	10 to 2.5	Below 2.5 Line	50	50					
Percentage of weights expected.....		2.5	7.5	15	25	25	15	7.5	2.5							
(1) Accidents Without Gross Hemorrhage																
(I) Ill less than 24 hours:																
(B) Additional disease	162	7	8	13	18	22	16	7	9	6	14.00	0.02		46	54	
(II) Ill 1 day or more:																
(A) No additional disease.....	175	3	8	12	24	26	13	8	6	6	4.33	0.55		47	53	
(B) Additional disease	187	10	9	19	17	21	12	9	3	6	22.84	0.00		55	45	
(2) Trauma With Gross Hemorrhage																
(I) Ill less than 24 hours:																
(A) No additional disease.....	489	1	1	11	16	29	23	13	6	6	112.49	0.00		29	71	
(B) Additional disease	70	5	6	9	14	30	16	10	10	4	7.83	0.05		34	66	
(II) Ill 1 day or more:																
(A) No additional disease.....	92	3	5	17	19	23	23	7	3	4	6.01	0.11		44	56	
(B) Additional disease	34	3	9	6	17	32	21	9	3	2	9.94	0.10		35	65	
(3) Poisoning with Heavy Metals																
(I) Ill less than 24 hours:																
(A) No additional disease.....	23	0	4	17	18	22	35	4	0	2	1.08	0.30		39	61	
(B) Additional disease	18	0	6	22	22	22	22	6	0		50	50	
(II) Ill 1 day or more:																
(A) No additional disease.....	14	7	7	7	29	36	7	7	0		50	50	
(B) Additional disease	6	

can the reduction of the liver. They also indicate why the older standards are lower than those presented here, and the age changes are different, even when care was taken to exclude all directly diseased organs (Greenwood,³ Greenwood and Brown,⁴ Bean and Baker,⁵ and Bean⁶).

COMMENT

The chief value of the charts presented here as standards of the normal weight of the liver and the spleen, over and above the means with their standard errors for age periods, is that they make it possible to compare a small series of cases from both sexes and covering the total adult age range without any subdivision of the data. In many disease conditions a series of 50 cases is large. If this group has to be divided into two sex groups, then into two or three age groups, the various groups become too small for reliable statistical comparison of the means. Moreover, the weights for a given disease can be plotted on the standards, as the data are gradually collected and an impression of the age and sex trend of the weight of the liver and the spleen in that disease gained before sufficient data are collected to justify the tedious calculations of means and standard deviations.

In using these charts it should be remembered that associated massive hemorrhage will lower the weights; that in wasting diseases most organs are reduced in weight; that if death in a given disease usually occurs with the spleen dilated, the weights will tend to fall in the upper zones, and conversely, if death consistently occurs with the spleen contracted, the weights will tend to fall in the lower zones; that while the 97.5 percentile line may be considered an approximation of the upper limit of normal variability, two to three weights in every hundred of weights in normal subjects, as can be judged by ordinary pathologic diagnosis, will be expected to fall above this line, and that the standards for females are not highly reliable, owing to the small number of cases.

SUMMARY

1. Graphic standards of the normal variability in the weight of both the liver and the spleen for both sexes for the age period from 20 to 80 years have been presented. These standards were constructed from the weights of livers and spleens from persons dying within twenty-four hours of injury, of trauma without any associated gross hemorrhage, of suffocation, of drowning, of electrocution or of poisonings by such substances as carbon monoxide, narcotics, hydrocyanic acid, strychnine and alcohol, and having no history of illness or any disease demonstrable at necropsy except moderate arteriosclerosis and such evidence of old healed infections as pleural adhesions.

2. When compared with these standards, the weights of both the liver and the spleen were materially reduced in persons dying of trauma accompanied by massive hemorrhage.

3. From these charts the deviation of the weights of the liver or the spleen in a given disease condition from the normal range of weights may be determined by plotting the weights on these standards and testing for the significance of the deviation of the observed from the expected number by the Chi-square method.

4. To these standards of normal variability in weight there have been added for the liver 500 Gm. zones of degrees of hypertrophy, and for the spleen, 100 Gm. zones.²⁵

25. Photolithic reproductions of charts 7 and 8, such as are being used in Dr. Barron's study, can be obtained at cost (approximately \$5 for 200 charts) by writing to the author. If preferred, similar charts may be constructed on any desired scale from tables 2 and 3.

NEGATIVE RESULT FROM TRANSFER OF MATERIAL FROM HUMAN ACUTE MULTIPLE SCLEROSIS TO MACACUS RHEBUS UNDER OPTI- MUM CONDITIONS

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AND

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The etiology of the large group of human diseases associated with disseminated foci of demyelination attacking mostly the white matter of the central nervous system is, as yet, unknown. Neuropathologic studies have served to differentiate certain types which, however, do not fall into clearcut clinical categories. Such studies also reveal that the tissue reactions in the several types are compatible with the inflammatory states called forth by infectious agents, and suggest that multiple sclerosis, Schilder's disease, disseminated encephalomyelitis and vaccinal encephalitis should be assumed to be of infectious origin and studied accordingly. Pathologic research has not shown them to be noninfectious.¹

Material from persons with any type of encephalitis is rarely obtained in the fresh state, unformaldehydized. Optimum conditions for culture or for experiments in the transmission of the disease to monkeys include the availability of fresh brain from a subject with an acute and rapidly progressing disease, aseptically removed a short time after death. When such conditions are met, we believe the results, although negative, are important for record. We present this case from nine others of a similar negative nature because of the uniquely favorable situation for study.

REPORT OF CASE

H. K., a woman, aged 22, entered the University of Chicago Clinics on April 26, 1932, complaining of periodic attacks of headache, dizziness and vomiting occurring once or twice a year for five or six years. During the last month there appeared staggering to the left, diplopia, transient and recurrent left-sided numbness, weakness of the right side of the face and jaw, and twitching of the right leg. Lying on the right side produced dizziness and nausea; on the left side, tinnitus in the left ear.

The investigation was carried on with the aid of a grant from the Josiah Macy Jr. Foundation.

From the Department of Hygiene and Bacteriology and the Division of Neurology and Neurosurgery of the University of Chicago.

1. Grinker, R. R., and Bassoe, P.: Disseminated Encephalomyelitis and Its Relation to Other Infections of the Central Nervous System, *Arch. Neurol. & Psychiat.* 25:723 (April) 1931.

Physical examination showed anisocoria, coarse horizontal nystagmus to the right and fine, rapid nystagmus to the left and up. Diplopia was produced by a weak right external rectus muscle. The jaw deviated to the left, and the left side of the face had a reduction in all sensory modalities. Hearing was diminished in the left ear, and there was peripheral facial weakness on the left side. Terminal action tremor and adiadosokinesis developed in the left arm, and in that extremity all sensory qualities were diminished. The flexors of both legs were weak; on the left, tone was increased and an action tremor was present. The lower deep reflexes were exaggerated, and a bilateral positive Babinski sign and patellar and ankle clonus were elicited.

The disease progressed rapidly with an increase in severity of all the signs and symptoms. In addition, retention of urine developed, the left arm became spastic and then a quadriplegia developed. Vomiting, difficulty in speaking and swallowing, and increasing lethargy indicated a bulbar and encephalitic extension. The patient died on May 26, with terminal bronchopneumonia and urinary infection.

The Wassermann reactions of the blood and spinal fluid were negative. The pressure of the cerebrospinal fluid was normal, and there were 10 lymphocytes per cubic millimeter. The protein content was only 47 mg. per hundred cubic centimeters. The benzoin curve showed a rise in the middle zone. The leukocyte count for the blood was only 7,600 per cubic millimeter.

Necropsy.—Evidences of a moderately severe infection of the urinary tract were found. There was bilateral bronchopneumonia, which was the cause of death. The brain and the spinal cord were removed within one hour after death. There was an excess of cerebrospinal fluid in the basal cisterns. The surfaces of the brain were flattened and edematous. The vessels of the leptomeninges and of the external and internal surfaces of the brain were extremely engorged with blood.

Histologic Examination.—Numerous blocks from the brain, brain stem and spinal cord were examined, the special staining methods being used to demonstrate myelin sheaths, fat, nerve fibers, cells and connective tissue.

The essential lesions were distributed irregularly throughout the central nervous system, including the brain and the brain stem, but were more numerous in the medulla and in the spinal cord. They were sharply limited to the white matter, not extending to the central gray matter or to the gray cortex. Myelin sheath stains showed them to be rather sharply outlined areas of complete demyelination. Scarlet *r* brought out the products of degeneration of myelin in the form of simple globules of fat, free in the tissue, included in the numerous proliferated microglia cells and within the intra-adventitial vascular spaces. The nerve fibers themselves were less severely affected, but within the areas of demyelination they were swollen and tortuous and many were fragmented. The glia were proliferated near the loci, and the ganglion cells nearby showed marked degenerative changes. Many of the blood vessels in the damaged areas were infiltrated with lymphocytes and an occasional plasma cell and polymorphonuclear leukocyte. The perivascular connective tissue was increased.

TRANSMISSION AND CULTURE EXPERIMENTS

Pieces of nerve tissue were taken aseptically from the cortex, pons and spinal cord and separately ground in covered sterile mortars with 3 cc. of sterile broth. Intracerebral injections of the individual specimens were made into three monkeys and of pooled material into a fourth monkey. One rabbit and three guinea-pigs were given injections of

the pooled specimen, the rabbit intracerebrally and the guinea-pigs intraperitoneally and subcutaneously. The rabbit and guinea-pigs were discarded after a month's observation, during which there was no abnormal temperature, local lesion or abnormal behavior. The temperature of the monkeys was recorded daily for over a month without significant variation from normal. They were killed by inhalation of ether ten months after inoculation; meanwhile they appeared normal in every respect. The brains and spinal cords were placed immediately in a diluted solution of formaldehyde, U. S. P. (1:10). Blocks were removed from various loci and cut and stained to demonstrate cells, myelin sheaths and fat. Grossly and histologically, there was not the slightest deviation from normal.

Bacteriologic examinations were made of the individual specimens. By means of Pasteur pipets, tissue emulsions were added to an assortment of special and routine mediums incubated under a variety of conditions. Extreme precautions were taken in the technic, and all materials were controlled for sterility. A green-producing streptococcus was grown from the cortical tissue, a pleomorphic streptococcus from the pons and *Staphylococcus albus* from the three sources. While it must be remembered that this patient died of bronchopneumonia, these bacteriologic findings cannot be attributed solely to an antemortem or even an agonal systemic infection. Our experience in the bacteriologic study of the group of cases of encephalitis and of a series of twelve controls of fresh material from the brain of patients dying of somatic diseases leads us to think that it was almost impossible to avoid occasional contamination by bacteria from the air. We base this opinion on the numbers and kinds of bacteria grown on blood agar plates exposed to the air in the small room in which the bacteriologic work was done. Specifically, we have isolated from the air the same bacteria that were grown from the brain and spinal cord in this case. For these reasons we attach no significance, as regards the cerebral condition, to our bacteriologic findings.

CONCLUSION

Material from the brain and spinal cord in an acute and rapidly fatal case of multiple sclerosis cultured and inoculated intracerebrally into monkeys gave entirely negative results.

Laboratory Methods and Technical Notes

A RAPID METHOD FOR THE DEMONSTRATION OF RETICULUM AND COLLAGEN FIBERS IN FROZEN SECTIONS

ARAM A. KRAJIAN, LOS ANGELES

A number of methods have been devised for the demonstration of reticulum fibers in tissue sections by silver impregnation. The method of Bielschowsky¹ was useful but time-consuming. In 1921, Perdrau² published a modification of Bielschowsky's technic which cut the time required in half, i. e., from about eight days to four. Frozen sections were used in both methods. More recently, Foot³ published a rapid method requiring the use of paraffin sections of tissue fixed in Zenker's solution. His method consumes about an hour's time after the sections are fixed to the slides.

In the method to be described the time required is about an hour and a half after the frozen sections have been cut. The advantages of this method consist not only in the ease and rapidity with which the technic can be carried out, but also in the sharp differentiation which results between the reticulum fibers and the collagen fibers. The reticulum becomes jet black and appears very sharp, while the coarse collagen fibers are deep brown. This results in a colorful picture which does not require counterstaining to demonstrate the connective tissue, although counterstaining can be done, as, for example, with van Gieson's solution.

1. Fix the tissue in a diluted solution of formaldehyde, U. S. P. (1:10) in the usual manner.
2. Cut the frozen sections from 5 to 10 microns thick.
3. Wash the sections in three changes of distilled water.
4. Place them in a 10 per cent solution of ammonium hydroxide heated at 60 C. for fifteen minutes. The bottom shelf of the paraffin oven is a good place for the small Stender dishes used.
5. Wash the sections in three changes of distilled water.
6. Place them in a 0.3 per cent solution of potassium permanganate for five minutes.
7. Wash them in distilled water for a few seconds.
8. Decolorize them in a 1.5 per cent solution of oxalic acid until all the brown color has disappeared. Sections should not be left in this solution longer than necessary. Each section should be treated separately.
9. Wash them thoroughly in four or five changes of distilled water.
10. Place them in a 5 per cent solution of silver nitrate kept at 60 C. in the paraffin oven for one hour.

1. Bielschowsky, Max: Anat. Anz. **36**:401, 1910.

2. Perdrau, J. R.: J. Path. & Bact. **24**:117, 1921.

3. Foot, N. C.: J. Tech. Methods **12**:117, 1929.

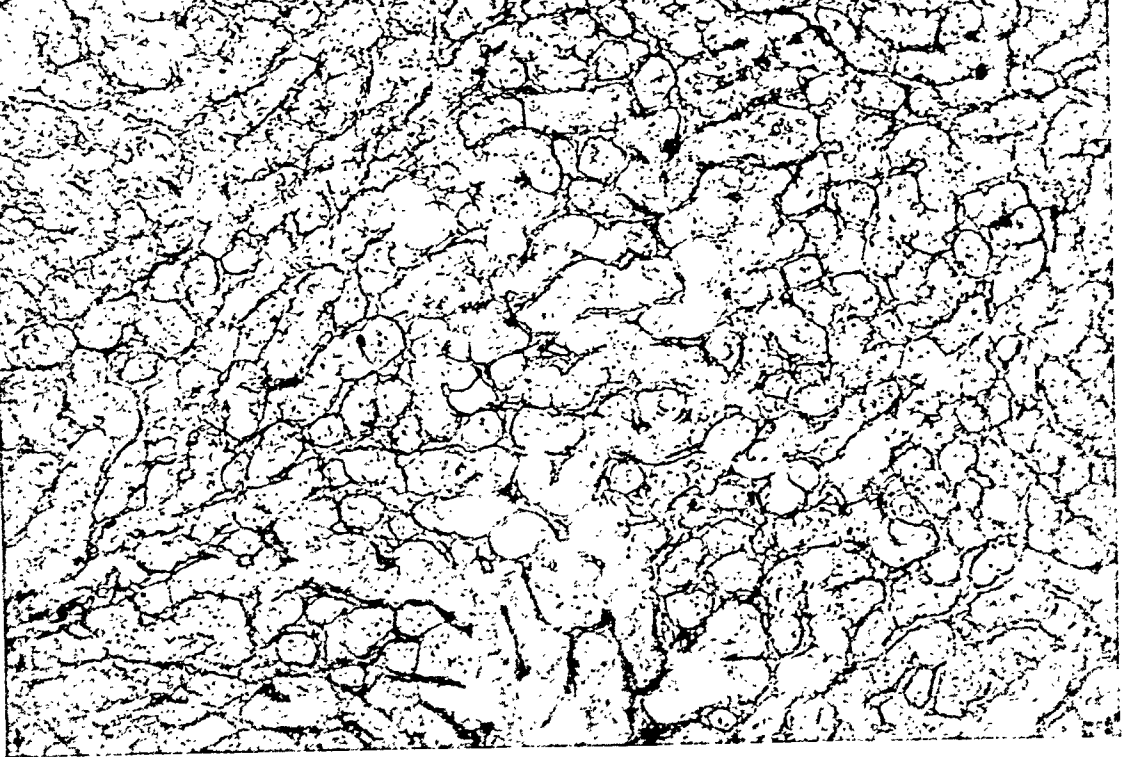


Fig. 1.—Human liver showing fine reticulum with reticulum stain; $\times 300$.

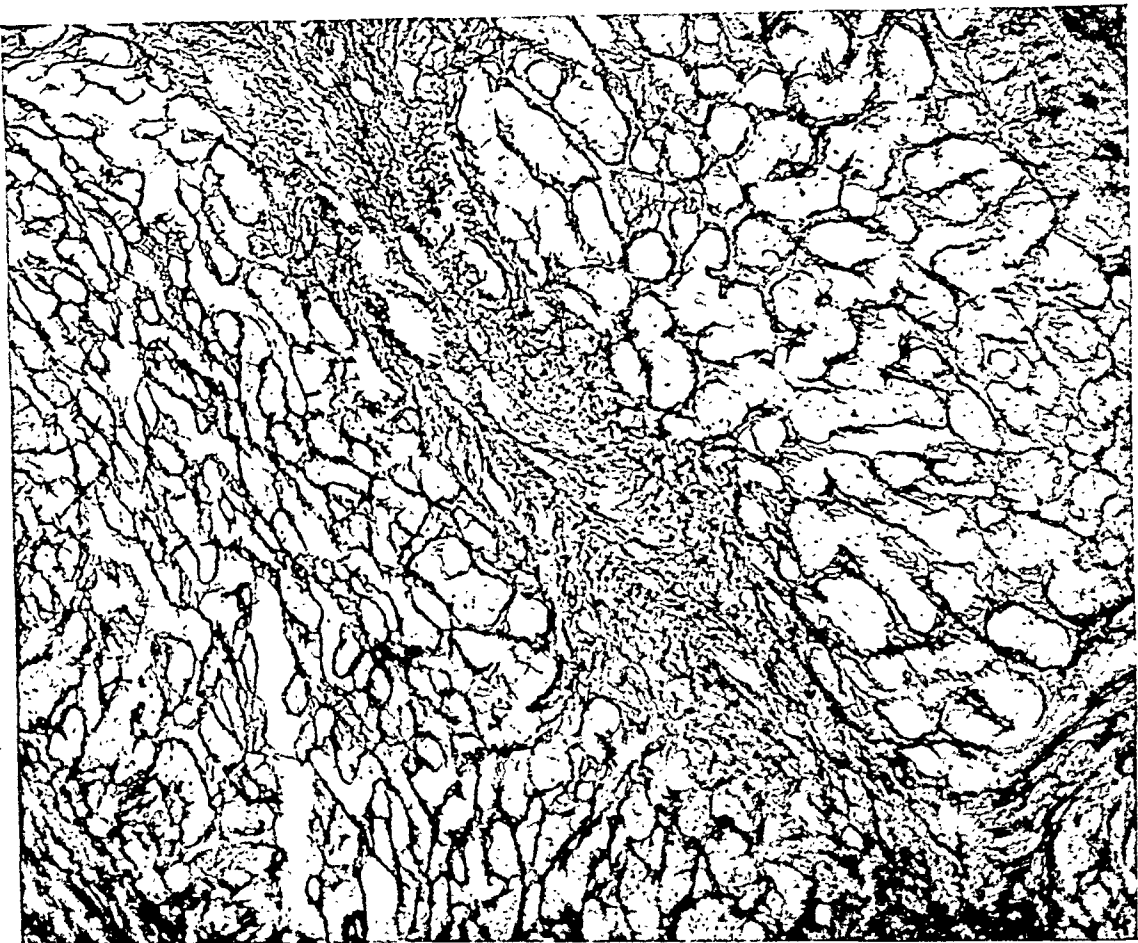


Fig. 2.—Cirrhosis of the human liver; $\times 300$.

11. Wash them in two changes of distilled water.

12. Place the sections in a solution of ammoniacal silver nitrate heated at 60 C. for fifteen minutes. The ammoniacal silver solution is prepared as follows:

Take 8 cc. of 10 per cent solution of silver nitrate. Add 6 drops of 10 per cent solution of sodium hydroxide. A brownish-black precipitate forms. Make up a fresh 10 per cent solution of ammonium hydroxide. Add this to the precipitated silver solution drop by drop until it is almost entirely cleared. Only a few small particles of the brownish-black precipitate should be allowed to remain. Then dilute it up to 28 cc. with distilled water. The resulting solution constitutes the ammoniacal silver.

13. Wash the sections quickly in three changes of distilled water.

14. Place them in a 30 per cent solution of formaldehyde (30 cc. of 40 per cent solution of formaldehyde plus 70 cc. of distilled water) heated at 60 C. from one to three minutes.

15. Wash the sections in a large basin of tap water and snatch onto slide.

16. Cover the section with a few drops of absolute alcohol and blot into position.

17. Complete the dehydration with two changes of absolute alcohol, blot, clear in equal parts of aniline oil and xylene for three minutes, wash in xylene and mount in gum damar or neutral Canada balsam.

If photomicrographs are desired, it is better to subject the section after step 14 to a toning process in a solution of gold chloride as follows:

1. Place the sections in a solution of gold chloride in distilled water 1:300 for from three to five minutes.

2. Wash them in distilled water and place in a 5 per cent solution of sodium hyposulphite (thiosulphate) from three to five minutes.

3. Then proceed with step 15.

This removes the brownish tint of the collagen fibers and cellular structures, leaving the collagen fibers a dull reddish purple.

SUMMARY

A rapid method for the demonstration of reticulum and collagen fibers in frozen sections is described. It has advantages over Perdrau's method in that (a) it is more rapid and (b) the collagen fibers appear dark brown, thus affording a colorful picture not requiring the use of a counterstain. If desired for photographic purposes, sharper contrast can be secured by a toning process.

From the Los Angeles County General Hospital.

General Review

RELATION OF THE SUPRARENAL GLANDS TO RESISTANCE

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AND

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. NEW YORK

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- IV. The Cortical Hormone and Natural Resistance.
- V. Significance of the Depression in Natural Resistance Following Suprarenal-ectomy.

There is a great deal of evidence both from morphologic and from physiologic studies that the suprarenal glands play a significant rôle in the defensive mechanism of the body, particularly against intoxications and infectious diseases. The active participation of the suprarenal cortex in this process has long been suspected by pathologists. Hyperemia, edema, hemorrhage and focal necrosis occur in the suprarenal glands in cases of burns of the skin, food poisoning and acute infections.

The suprarenal glands of guinea-pigs poisoned with diphtheria toxin or arsenicals are severely injured (Roux and Yersin¹). In a study of 2,800 guinea-pigs killed by injections of diphtheria toxin, Rosenau and Anderson² were able to confirm these observations.³ Distemper in cats

From the Laboratory Division, Montefiore Hospital, and the Department of Pathology, School of Medicine, Cornell University.

1. Roux, E., and Yersin, A.: *Ann. Inst. Pasteur* **3**:273, 1889.

2. Rosenau, M. J., and Anderson, J. F.: *A Stomach Lesion in Guinea Pigs Caused by Diphtheria Toxin and Its Bearing upon Experimental Gastric Ulcer*, U. S. Hyg. Lab. Bull. no. 22, 1906.

3. Gastric ulcers and erosions were present in almost two thirds of these pigs (Marine, David: *Some Effects of Suprarenal Injury on Natural and Acquired Resistance*, in *Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues*, New York, International Press, 1932). Rosenau and Anderson² could not have known that similar ulcers regularly occur following removal or severe injury of the suprarenals in the dog, cat, rabbit, guinea-pig and rat. Marine expressed the belief, based on experimental observations, that the ulcers seen in severe burns and in diphtheria poisoning are associated with the severe suprarenal cortical injury occurring in such conditions.

is associated with injury to the suprarenal cortex. Marine⁴ observed that the lesions begin as focal necrosis of the cells of the reticular and fascicular layers but as a rule do not extend to the glomerular zone. With recovery, calcification of the necrotic areas occurs in a large percentage of cats. Calcification was observed in the cortex in 25 per cent of a series of 257 cats. In influenza and in peritonitis, focal necrosis of the cortex occurs. Influenzal asthenia may be associated with suprarenal injury. The amount of cholesterol and its esters in the cortex is greatly decreased during acute infectious diseases.⁵ These observations led to the view that the suprarenal cortex is concerned directly or indirectly with the neutralization of toxins. It was noted that patients suffering from Addison's disease succumb readily to drugs and toxins in amounts generally innocuous to a normal person.

Status lymphaticus, since the work of Wiesel,⁶ Hedinger,⁷ Paltauf⁸ and others, has been shown to have some important relation to the suprarenal glands. The marked hyperplasia of the thymus and of the lymphoid tissue following experimental suprarenal insufficiency in rats and cats was first pointed out by Jaffe,⁹ and the similarity of this experimental condition to human status thymicolymphaticus was emphasized by these investigators. Status lymphaticus is particularly associated with the cortex. Both in status lymphaticus and in experimental suprarenal insufficiency there are lowered resistance to poisons and marked changes in temperature.¹⁰

I. RELATION OF THE SUPRARENAL GLANDS TO THE FORMATION OF ANTIBODIES

Experiments dealing with the antibody-forming capacity of animals following bilateral suprarenalectomy have been limited because of technical difficulties. Immunologic studies bearing on this subject may be divided into two groups: (1) those on the effect of injections of epinephrine into the normal animal on the complement titer and on the formation of antibodies, and (2) those on the influence of partial or complete suprarenalectomy on the formation of antibodies.

Josué and Paillard¹¹ studied the opsonic properties of rabbits' blood after the intravenous injection of epinephrine and found that

4. Marine, David: *J. Exper. Med.* **43**:495, 1926.

5. Aschoff, L.: *Lectures on Pathology*, New York, Paul B. Hoeber, Inc., 1924, p. 101.

6. Wiesel, J.: *Internat. Clin.* **2**:288, 1905.

7. Hedinger, E.: *Frankfurt. Ztschr. f. Path.* **1**:527, 1907.

8. Paltauf, R.: *Wien. klin. Wchnschr.* **2**:877, 1889; **3**:172, 1890.

9. Jaffe, H. L.: *J. Exper. Med.* **40**:325, 619 and 753, 1924.

10. Marine, David: *Arch. Path.* **5**:661, 1928.

11. Josué, O., and Paillard, H.: *Compt. rend. Soc. de biol.* **68**:657, 1910.

this drug was without effect. The production of sheep cell hemolysins and of typhoid agglutinins in rabbits following the subcutaneous and intravenous administration of epinephrine was studied by Bijlsma¹² and Hrma.¹³ No appreciable effect was obtained. Bijlsma¹² observed also that unilateral suprarenalectomy in rabbits was without influence on the production of hemolysins and agglutinins. A decrease in the complement titer of the serum of guinea-pigs after the administration of epinephrine and atropine was reported by Pinner.¹⁴ Ecker and Rogoff¹⁵ found no change in the complement titer of the blood of rabbits which survived double suprarenalectomy. The observations of Ecker and Rogoff were confirmed by Také and Marine¹⁶ in suprarenalectomized rabbits. Hektoen and Curtis¹⁷ removed the suprarenal glands from normal dogs and from dogs in which the antibody curve was at its height and found that no change in the curve followed. Gates¹⁸ studied the formation of hemolysins and agglutinins in guinea-pigs and in 3 rabbits after the removal of from three fourths to seven eighths of the suprarenal glands. He observed no noteworthy effects. Také and Marine¹⁶ found that rabbits which have survived removal of both suprarenal glands have higher hemolysin titers than normal rabbits. The highest titer in a series of 30 normal rabbits was 1,500, or the same as the lowest titer in 14 suprarenalectomized rabbits. The average titer for the suprarenalectomized rabbits was more than twice that for the normal animals. Také and Marine could find no explanation of the increase in the formation of hemolysins, but they expressed the belief that it is associated with a loss of the cortex rather than of the medulla. They suggested that the disturbance in the formation of antibodies is due to a loss of some regulatory and inhibitory influence which the cortex normally exerts on the irritability and susceptibility of the cells of the body. In subsequent experiments Jaffe and Marine¹⁹ studied the effect of suprarenalectomy on the formation of agglutinins in rats.

The studies included 30 bilaterally suprarenalectomized and 3 unilaterally suprarenalectomized rats, 4 animals in which the perisuprarenal tissue was traumatized and 31 controls. The rats that had been operated on were repeatedly inoculated with typhoid vaccine in amounts of 0.2 cc. between eight and forty days after suprarenalectomy. Three or four injections were given at three day intervals. Titrations were made every third or fourth day after the last injection.

12. Bijlsma, U. G.: *Centralbl. f. Bakt. (Abt. 1)* **86**:246, 1921.

13. Hrma, A.: *Casop. lék. cesk.* **61**:1217, 1922.

14. Pinner, M.: *Beitr. z. klin. d. Tuberk.* **46**:471, 1920.

15. Ecker, E. E., and Rogoff, J. M.: *J. Immunol.* **6**:355, 1921.

16. Také, N. M., and Marine, David: *J. Infect. Dis.* **33**:217, 1923.

17. Hektoen, L., and Curtis, A. R.: *J. Infect. Dis.* **17**:409, 1915.

18. Gates, F. L.: *J. Exper. Med.* **27**:725, 1918.

19. Jaffe, H. L., and Marine, David: *J. Infect. Dis.* **35**:334, 1924.

It was found that rats immunized with typhoid vaccine within three weeks following bilateral suprarenalectomy had agglutinin titers averaging from two to three times greater than those of the controls. Six weeks after suprarenalectomy no difference in the formation of agglutinins could be determined between normal animals and suprarenalectomized rats surviving the operation in good condition, although the resistance of the latter to large doses of vaccine was still below normal. These findings were at variance with those of Khorazo, who observed no essential difference in the formation of agglutinins between normal and suprarenalectomized rats.¹⁹ Marine found that suprarenal-ectomized rabbits form antitoxin to diphtheria toxin as rapidly as or more rapidly than the controls. The antitoxin formation was determined by repeated Schick tests.

The formation of antibodies in suprarenalectomized rats was studied by Perla and Marmorston-Gottesman in a series of experiments.²⁰

In preliminary studies on the formation of hemolysins in normal rats ^{20a} it was found that high titers were obtained following a single intraperitoneal injection of a small amount of sheep cells (1 cc. of a 10 per cent suspension). This rapid method of immunization is definitely advantageous in studying the formation of antibodies in the early period after bilateral suprarenalectomy.^{20b} The titer was determined five, eight, eleven and fourteen days after the injection. It was found that the antibody titer varied with the quantity of antigen injected, and the antigen-antibody curve for normal rats was first determined.

In the first group of experiments we determined the influence on the titer of varying the time between suprarenalectomy and the injection of antigen, keeping the amount of antigen injected constant. In the second group of experiments the quantity of antigen injected was varied, but the time after suprarenal-ectomy was kept constant. In about 70 per cent of the rats the titer was above 1:2,000, and the average titer for 43 normal rats was 1:5,600.^{20c} In a large series of suprarenalectomized rats, a study was made of the formation of hemolysins in response to a fixed amount of sheep cells (1 cc. of a 10 per cent suspension) injected intraperitoneally forty-eight hours and seven, fourteen and twenty-eight days after operation. The formation of hemolysins was studied in suprarenalectomized rats which two weeks following the operation were given injections of one-twentieth and of ten times this amount. The formation of hemolysins was studied in rats which were traumatized by tearing the perisuprarenal tissue and two weeks after the operation were given an injection of 1 cc. of a 10 per cent suspension of sheep cells, and the results were compared with those in the normal control rats. The effect of the operative procedure was controlled by removing one kidney in a series of rats and determining the antibody response to sheep cells.

Bilateral suprarenalectomy in rats which subsequently were given intraperitoneally 1 cc. of a 10 per cent suspension of sheep cells resulted in a depression of the hemolysin titer during five weeks following the

20. (a) Marmorston-Gottesman, J., and Perla, David: *J. Exper. Med.* **47**:713, 1928; (b) **47**:723, 1928; (c) **48**:225, 1928; (d) **50**:87, 1929; (e) **50**:93 1929.

operation, the depression being most marked during the second week. When 1 cc. of undiluted sheep cells was injected intraperitoneally two weeks after the operation, bilaterally suprarenalectomized rats gave hemolysin titers higher than those of normal rats. The quantity of antigen necessary to yield the maximum titer in suprarenalectomized rats two weeks after operation is ten times the quantity necessary to yield the same titer in normal rats. Traumatization of the perisuprarenal tissue in rats resulted in a decrease in the formation of hemolysins which was even more prolonged than in a corresponding series of suprarenalectomized rats. Traumatization of the perisuprarenal area probably results in severing or injuring the sympathetic or parasympathetic nerves innervating the suprarenals. This injury may cause a depression of the function of the cortex as well as of the medulla.

Though it is well known (Dreyer,²¹ Tscheboksaroff²² and Stewart and Rogoff²³) that the output of epinephrine from the suprarenal glands is controlled by a nervous mechanism, and that interruption of the nerve pathway results in a diminution of the output, the extent of the nervous control of the function of the cortex is undetermined. Depression of the antibody-forming capacity to small amounts of antigen may be an expression of impaired suprarenal function. However, with the removal of the suprarenal glands in rats, regeneration of thymic and lymphoid tissue occurs.⁹ This hyperplasia does not occur following traumatization of perisuprarenal tissue. This lymphoid hyperplasia may be in some way responsible in suprarenalectomized rats for the partial recovery of the antibody-forming capacity several weeks after operation.

Though injections of epinephrine^{20d} raise the antibody-forming capacity in suprarenalectomized rats, the diluting fluid, isotonic solution of sodium chloride, was found to have a similar effect. Experiments on a large series of rats demonstrated that repeated injections of large amounts of an isotonic solution of sodium chloride or of sodium acetate restore the antibody titer of suprarenalectomized animals to normal.^{20c} The effect of these solutions is not due to diuresis alone, since isotonic dextrose solution does not affect the titer, or to the sodium ion alone, since hypertonic solutions of sodium chloride in small volume have little influence on the titer. It would seem from these observations that both the fluid and the sodium ion are necessary to bring about a restoration of the antibody-forming capacity of suprarenalectomized rats to normal.

These results are in accord with those of Marine and Baumann,²⁴ who found that the administration of Ringer's solution and of isotonic solutions of sodium chloride and sodium acetate increased the duration

21. Dreyer, G. P.: *Am. J. Physiol.* **2**:203, 1899.

22. Tscheboksaroff, M.: *Arch. f. d. ges. Physiol.* **137**:59, 1911.

23. Stewart, G. N., and Rogoff, J. M.: *J. Exper. Med.* **26**:613, 1917.

24. Marine, David, and Baumann, E. J.: *Am. J. Physiol.* **81**:86, 1927.

of life of suprarenalectomized cats threefold. Isotonic solutions of dextrose and of glycerin had only a slight life-prolonging effect.

It is well known that the sodium ion plays an important rôle in the water exchange in the tissues. Suprarenalectomy results in a profound disturbance of the water balance. Following removal of the glands, there are a loss of fluid through the intestines, a diminution of the sodium content of the blood (Baumann and Kurland ²⁵) and an impairment of renal function. These factors result in dehydration of tissues and in a disturbance of the normal cellular physiologic activity. It is possible that the elements in the tissues concerned with antibody formation respond to a lesser degree in the production of immune bodies in suprarenalectomized rats than in normal rats. There may, however, be no actual loss of production of immune bodies, but a diminished release of these antibodies into the blood stream. The injection of large quantities of fluid containing isotonic solutions of sodium salts restores the water balance in the body to normal by promoting diuresis and supplying fluid in a form that can be retained in the tissues. The antibody-forming mechanism is thus restored to normal. The rôle of the suprarenal gland in the formation of antibodies appears to be intimately connected with the maintenance of water balance. This observation is of importance in the interpretation of certain phenomena in acute infections. It is a matter of empiricism that forcing fluids is beneficial in the treatment of severe infections and of extensive burns of the skin. It is known that in burns and in many acute infections the suprarenal glands are severely injured. The injury may result in a disturbance of the water balance of the tissues and of the antibody-forming capacity of the body. This disturbance may be corrected to some extent by the parenteral and oral administration of large quantities of physiologic solution of sodium chloride.

It may be concluded that suprarenalectomy is followed by a disturbance in the antibody-forming mechanism of the tissues. The suprarenal gland plays a rôle in the water metabolism of the tissues. Restoration of the water exchange to a normal level is sufficient to restore the antibody-forming capacity to normal. The rôle of the suprarenal cortex in the formation of antibodies is therefore an indirect one, dependent on the influence of the cortex on the water balance in the tissues.

II. RELATION OF THE SUPRARENAL GLANDS TO ANAPHYLAXIS

Képinow ²⁶ found that the removal of one suprarenal gland and of the greater part of the other makes guinea-pigs more susceptible to anaphylactic shock, especially to active anaphylaxis.

25. Baumann, E. J., and Kurland, Sarah: *J. Biol. Chem.* **71**:281, 1927.

26. Képinow, L.: *Compt. rend. Soc. de biol.* **87**:327, 1922.

Ten unilaterally suprarenalectomized guinea-pigs and seven normal controls were sensitized with horse serum, and from sixteen to eighteen days later the other suprarenal gland of the animals operated on previously was partially removed. Six days after the second operation, varying amounts of horse serum were injected intra-arterially both into the suprarenalectomized animals and into the controls. The normal animals presented the symptoms characteristic of anaphylactic shock and died following the injection of 0.1 cc. of horse serum. The animals that had been operated on were killed by 0.025 cc. of horse serum. In another series of guinea-pigs, the removal of one gland and part of the other was done at the same time; the animals were sensitized with an injection of serum fifteen days later, and subsequently tested as in the first series. The controls were killed by a second injection of 0.2 cc. of horse serum, and the animals that were operated on succumbed after an injection of 0.025 cc., one eighth the amount necessary to kill a normal guinea-pig. In guinea-pigs passively sensitized by the injection of serum of rabbits actively sensitized to horse serum, the amount of serum necessary to produce shock was the same in the controls as in the animals with suprarenal insufficiency.

Bilaterally suprarenalectomized rats show markedly increased susceptibility to anaphylactic shock produced by intraperitoneal injections of horse serum (Flashman,²⁷ Wyman²⁸). This effect is obtained whether the animals are sensitized before or after suprarenalectomy.

The normal albino rat is very resistant to anaphylaxis. This reflects in part the high degree of natural resistance to all toxins and poisons, but the rat is known to form precipitins poorly (Longcope). Parker and Parker, however, in 1924, showed that anaphylactic shock can be produced in the white rat after both active and passive sensitization.

In studying the relation of suprarenal insufficiency to anaphylaxis, Wyman²⁸ used adult rats, from 5 to 12 months old. The rats were sensitized by giving three intraperitoneal injections of 1 cc. of horse serum at two day intervals. The test dose of 1 cc. of horse serum was given on the tenth, eleventh or twelfth day after the last sensitizing dose. Of 25 doubly suprarenalectomized rats sensitized with horse serum, 36 per cent died of anaphylactic shock following the test dose, 20 per cent had severe symptoms, and 32 per cent had slight symptoms. In 12 of the cases, the first sensitizing dose was given from twelve to sixteen days after suprarenalectomy. The test dose was given from twenty-three to twenty-seven days after operation. Following the test dose, 5 of the 12 animals had slight symptoms, 2 had moderate symptoms, 3 had severe symptoms (2 of these died in twelve hours), and 2 died sixty and one hundred and forty-seven minutes after the injection.

In the 13 other cases the first sensitizing dose was given from eighty-five to one hundred and sixty-eight days after suprarenalectomy and the test dose was given ten or eleven days later. Three animals had slight symptoms, 1 had moderate symptoms, 2 had severe symptoms, and 7 died from thirty to one hundred and forty-three minutes after the injection.

A group of 29 normal rats were sensitized by injections of horse serum and tested twelve days later. There were slight or no symptoms, and none of the

27. Flashman, D. H.: *J. Infect. Dis.* **38**:461, 1926.

28. Wyman, L. C.: *Am. J. Physiol.* **89**:356, 1929.

animals died. Of 15 of these rats which were suprarenalectomized after the test injection, 12 died of anaphylactic shock following the injection of a second test dose from seven to ten days after the operation. It is interesting that no correlation was found between the presence or absence of gross accessory cortical tissue or the time of survival after operation and the susceptibility to anaphylactic shock.

Of 15 suprarenalectomized rats having autoplasmic cortical transplants and in some cases gross accessory cortical tissue as well, 40 per cent died of anaphylactic shock following sensitization and the injection of a test dose of horse serum. From these experiments, Wyman concluded that the increased susceptibility to anaphylactic shock must be due to medullary insufficiency. An attempt to reduce the susceptibility of suprarenalectomized rats to anaphylactic shock by means of repeated injections of epinephrine chloride solution gave evidence of little or no protection.

The work of Wyman conclusively demonstrates the increased susceptibility of suprarenalectomized rats to anaphylaxis. The evidence does not prove that the medullary deficiency is responsible, though it may play a rôle.

The failure of cortical rests or transplants to protect does not exclude the fact that the normal cortex may be essentially responsible for the high degree of resistance of the rat to anaphylaxis. Though cortical rests in suprarenalectomized animals may function sufficiently to prolong life, they do not appreciably raise the resistance of these animals to severe intoxication. We have found this to be true in histamine poisoning. Nevertheless the administration of cortical hormone raises the resistance of suprarenalectomized rats to the level of normal rats.

III. RELATION OF THE SUPRARENAL GLANDS TO NATURAL AND ACQUIRED RESISTANCE

Though the increased susceptibility of suprarenalectomized animals to toxins and poisons was suggested in fragmentary, poorly controlled work by French investigators,²⁹ Lewis³⁰ first demonstrated, in 1921 and 1923, the marked sensitivity of suprarenalectomized rats to intoxication with cobra venom, curare, veratrine, papaverine, codeine, morphine, digitoxin, epinephrine and diphtheria toxin. There was no depression in the resistance of suprarenalectomized animals to picrotoxin and strychnine. He observed that the resistance is lowered soon after suprarenalectomy and gradually diminishes until it disappears. The resistance of suprarenalectomized rats to morphine is four hundred

29. Abelous, J. E.: *Compt. rend. Soc. de biol.* **47**:458, 1895. Boinet, E.: *ibid.* **48**:364, 1896. Langlois and Charrin: *ibid.* **48**:708, 1896. Oppenheim, M. R.: *ibid.* **53**:314 and 316, 1901.

30. (a) Lewis, J. T.: *Rev. Assoc. méd. argent.* **35**:529, 1921; (b) *Am. J. Physiol.* **64**:506, 1923.

times lower than that of normal rats. The problem was extensively studied in Marine's laboratory for many years. Scott³¹ confirmed the susceptibility of suprarenalectomized rats to morphine. Belding and Wyman³² extended the observations to diphtheria toxin and noted that rats without suprarenal glands were twice as susceptible as normal rats. Marked depression in resistance to typhoid vaccine was noted by Jaffe and Marine,¹⁹ and Jaffe³³ demonstrated a definite protective action afforded by autoplasmic transplants of cortical suprarenal tissue prior to suprarenalectomy. Further studies were made with cystine, glutathione and cyanides by Voegtlin, Johnson and Dyer,³⁴ and these confirmed the early work on the significance of the suprarenal cortex in resistance.

An effort to standardize a test for suprarenal insufficiency in the rat was made by Marmorston-Gottesman and Gottesman.³⁵ Of all the drugs thus far used in testing the resistance of suprarenalectomized rats, histamine was found to be most satisfactory. It is readily obtainable and comparatively stable and produces characteristic symptoms. The minimum lethal dose for a given strain of rats can be established within narrow limits, and the difference between the minimum lethal dose for normal and for suprarenalectomized rats is comparatively great (1:10). Banting and Gairns³⁶ found that suprarenalectomized dogs are about thirty times more susceptible to histamine than are normal dogs.

Marmorston-Gottesman and Gottesman³⁵ demonstrated the presence of a latent period after suprarenalectomy during which time resistance is still relatively high. The marked drop in resistance does not occur until about the fifth day after the operation. The height of susceptibility is reached between the fifth and eighth day.

Of 18 suprarenalectomized rats into which 100 mg. of histamine acid phosphate per kilogram was injected between the first and the fourth day after removal of both glands, only 5 were killed, whereas of 31 suprarenalectomized rats inoculated five, six, seven and eight days after operation, 24 were killed.

The resistance of suprarenalectomized rats is strikingly lowered during all periods after the operation, but the depression is greatest at the end of the first week. The drop in resistance occurs in all rats regardless of the presence of accessory cortical tissue. Such severe procedures as bilateral nephrectomy, however, fail to affect the resistance

31. Scott, W. J. M.: *J. Exper. Med.* **38**:543, 1923.

32. Belding, D. L., and Wyman, L. C.: *Am. J. Physiol.* **78**:50, 1926.

33. Jaffe, H. L.: *Am. J. Path.* **2**:421, 1926.

34. Voegtlin, Carl; Johnson, J. M., and Dyer, H. A.: *J. Pharmacol. & Exper. Therap.* **27**:467, 1926.

35. Marmorston-Gottesman, J., and Gottesman, J.: *J. Exper. Med.* **47**:503, 1928.

36. Banting, F. G., and Gairns, S.: *Am. J. Physiol.* **77**:100, 1926.

of the rat, though death supervenes in seven or eight days (Marmorston-Gottesman and Gottesman³⁷).

The use of the rat in studying problems of resistance following suprarenalectomy has many advantages. In our experience with rats from original Wistar Institute stock maintained in this laboratory for about ten years, under standard dietetic and environmental conditions the percentage of animals surviving bilateral suprarenalectomy for two weeks or longer was about 90. These observations are based on an experience with over 1,000 rats.

There are conflicting reports in the literature on the survival capacity of rats following suprarenalectomy. Most authors agree that a very large percentage of rats survive the removal of the suprarenals for a *considerably longer period than other mammals* (Lewis,^{30b} Scott,³¹ Jaffe and Marine,¹⁹ Jaffe,³³ Wyman,²⁸ Perla and Marmorston and others). Jaffe observed that in a series of 90 suprarenalectomized rats, 35 per cent died within thirty days, most of them before the thirteenth day; 46 per cent died in seven months, and 19 per cent remained unaffected and presented a large amount of accessory cortical tissue when killed.

Pencharz, Olmsted and Giragossintz,³⁸ on the other hand, observed that all of a series of 62 suprarenalectomized rats died in from two to eighteen days with no survivals beyond this period. Rats from 3 to 4 weeks of age were utilized by Kutz³⁹ for the determination of the potency of cortical extracts.⁴ He observed that 56 of 57 suprarenalectomized rats died by the tenth day. Freed, Brownfield and Evans⁴⁰ reported that suprarenalectomy in rats is fatal in all instances. Firor and Grollman,⁴¹ in a recently published article, concluded that the rat presents no exception to the fact that suprarenalectomy in mammals is fatal.

The survival capacity of rats following suprarenalectomy is dependent on the varying amounts of microscopic rests of cortical cells in the retroperitoneal space from the region of the suprarenal gland to the bifurcation of the aorta. Gross accessory tissue is not frequently observed, although serial sections of the retroperitoneal tissue show accessory cortical tissue in a very high percentage of rats. It is impossible to remove all the accessory cortical tissue, and one must, therefore, limit oneself to removal of the suprarenal glands if one is to observe

37. Marmorston-Gottesman, J., and Gottesman, J.: *Proc. Soc. Exper. Biol. & Med.* **24**:45, 1926.

38. Pencharz, R.; Olmsted, J. M. D., and Giragossintz, G.: *Physiol. Zööl.* **4**:501, 1931.

39. Kutz, R. L.: *Proc. Soc. Exper. Biol. & Med.* **29**:91, 1931.

40. Freed, S. C.; Brownfield, B., and Evans, H. M.: *Proc. Soc. Exper. Biol. & Med.* **29**:1, 1931.

41. Firor, W., and Grollman, A.: *Am. J. Physiol.* **103**:686, 1933.

the effects of this operation in the rat. The conflicting reports on the survival capacity of rats may be due in part to faulty technic in the operation. (Suprarenalectomy is extremely likely to produce shock and must be done skilfully with a minimum amount of trauma and tugging at the tissues.) The poor survival capacity may be due to careless after-care, as suprarenalectomized rats are extremely susceptible to the effects of cold. In extremely young rats (under the age of 4 weeks) a much higher mortality occurs than in older animals. At from 7 to 8 weeks of age rats show an excellent capacity for surviving the operation, in our experience, and the resistance may be somewhat higher than that of adult rats one week after operation. Undoubtedly, different strains of rats possess varying amounts of cortical tissue. It is possible that some strains possess no such accessory cortical tissue and do not survive suprarenalectomy any better than the larger mammals. There are other factors which may influence the period of survival of suprarenalectomized rats. We have observed that the use of an artificial diet adequate in all respects, according to present knowledge, seems to lower the capacity for survival of rats following the removal of the suprarenals. Of a series of 20 suprarenalectomized rats from 2 to 3 months old fed on our usual mixed diet of scraps of meat, hominy, rolled oats, milk, bread, salt and greens, 17 survived for a month, at which time they were killed. Of a group of 15 rats fed on a completely adequate artificial diet, composed of casein, cornstarch, yeast and MacCallum's salt mixture, butter fat, viosterol and orange juice, only 1 survived for three weeks, and of the remaining 14, 10 died from the seventh to the ninth day and 3 from the seventh to the twentieth day. Although artificial diets such as these may be adequate when gaged by curves of growth and by the reproductive capacity of the animals, under conditions of marked physiologic strain they may prove to be inadequate in some still unknown respect. The importance, therefore, of maintaining a uniform strain of rats bred in the laboratory and kept under identical environmental and dietetic conditions cannot be overemphasized.

It has been our experience from a large series of observations that in spite of the presence of microscopic cortical tissue in the rat, all rats of our stock one week after operation show a profound drop in the natural resistance to poisons and infections. Although the small amount of accessory tissue may be sufficient to maintain life for a comparatively long period, it is insufficient to maintain the normal natural resistance of the animal.

The decrease in the resistance of suprarenalectomized rats to poisons such as cyanide, nicotine, acetylcholine, histamine, curare, morphine, snake venom, diphtheria toxin, chloral hydrate and typhoid vaccine has been demonstrated by numerous investigators. The development of a test of the degree of suprarenal insufficiency in the rat, a mammal that

lends itself to laboratory standardization, was of considerable importance in later work in this field.

The study of the problem was broadened and extended into the field of infections by the work of Perla and Marmorston-Gottesman⁴² who studied the effects of suprarenalectomy on the resistance of the rat to a protozoan infection caused by *Trypanosoma lewisi* and to *Bartonella muris* anemia, two diseases native to the rat.

In the experiments with *T. lewisi*,^{42a} 18 adult rats were suprarenalectomized, and in 5 the suprarenal areas were traumatized. Six days after the operation each rat was given intraperitoneally 1 cc. of a 10 per cent dilution of whole blood drawn from a rat infected with *T. lewisi*. Counts of the trypanosomes in the peripheral blood were made at frequent intervals.

Sixty-seven per cent of the rats died from two to nineteen days after the injection. The average duration of life of the rats in which the infection proved fatal was five and eight-tenths days. Though the disease is fatal in about 70 per cent of suprarenalectomized rats, it is not fatal in normal rats. Despite this high mortality, the infection, as characterized by the rate of growth of the trypanosomes, does not differ essentially from the infection in normal rats. Neither the reproduction-inhibiting antibody (Taliaferro⁴³) nor the trypanolytic factor is diminished by suprarenalectomy. Apparently the *toxic* effect of the infection is lethal in these animals. Suprarenalectomy, further, diminishes the degree of splenic response as estimated by the size of the spleen but does not alter the reaction of the reticular and endothelial elements of the spleen or of the lymphoid tissue to infection with *T. lewisi*.

One infection with *T. lewisi* confers a permanent immunity on normal rats. It is of significance that suprarenalectomy does not break down the permanent immunity acquired as a result of a first infection. The natural susceptibility of the rat to various toxins, poisons and infections is markedly increased by suprarenalectomy. But the acquired immunity established as a result of a first infection is uninfluenced.

In subsequent communications further data were presented on the effect of bilateral suprarenalectomy in the rat on natural and acquired resistance to *B. muris* anemia.^{42b}

The rat is spontaneously infected with *B. muris* between the fourth and fifth weeks of life. It becomes a carrier and acquires immunity. The spontaneous recurrence of infection following splenectomy with the development of anemia

42. (a) Marmorston-Gottesman, J.; Perla, David, and Vorzimer, Jefferson: *J. Exper. Med.* **52**:587, 1930. (b) Marmorston-Gottesman, J., and Perla, David: *ibid.* **55**:109, 1932.

43. Taliaferro, W. H.: *The Immunity of Parasitic Infections*, New York, Century Company, 1929.

in the adult rat of carrier stock is indicative of a depression in the acquired resistance to *B. muris*. (For a review of this subject, see papers by Perla and Marmorston-Gottesman,^{42b} Lauda⁴⁴ and Reitano⁴⁵).

Ten rats, 3 months of age, were suprarenalectomized. On the sixth day after suprarenalectomy, each was given intraperitoneally 2 cc. of whole blood of anemic adult splenectomized rats. No anemia developed in any of the rats. Ford and Eliot⁴⁶ showed that 0.0001 cc. of blood of an anemic rat is sufficient to transmit the anemia to splenectomized rats of noncarrier stock. The suprarenalectomized rats of carrier stock, therefore, withstand a quantity of infecting material twenty thousand times as great as is sufficient to produce anemia in the splenectomized rat of noncarrier stock. The acquired resistance to *B. muris* conferred on rats of carrier stock by a first infection in early life, though strikingly depressed by splenectomy, is uninfluenced by suprarenalectomy.

The effect of suprarenalectomy on the natural resistance to *B. muris* was studied in rats of Wistar Institute stock, noncarriers of *B. muris*. In these rats splenectomy is not followed by *B. muris* anemia, but anemia will develop if they are subsequently exposed to rats of carrier stock for a few days. Of 10 suprarenalectomized rats of Wistar Institute stock, 8 died within three days following the injection of infective material and 2 on the fifth and sixth days. In most instances the rats died before sufficient time had elapsed for the development of severe anemia. Death was apparently caused by toxemia. In rats surviving longer than two days anemia developed. Though severe anemia developed after the injection of the same amount of infecting material into the control rats of Wistar stock that had not been operated on, all of these recovered. It is apparent that the natural resistance to infection with *B. muris* is lowered by suprarenalectomy. Although the rapidity with which the anemia developed was no greater nor was the disease more severe in the suprarenalectomized than in the normal rats, all the suprarenalectomized rats died of toxemia. (The mortality from *B. muris* anemia in splenectomized rats of carrier stock is about 30 per cent.) The nature of the rôle of the suprarenal glands in natural resistance to this infection is of a general character. There is no change in the type of reaction in the tissues following infection in suprarenalectomized rats, but there is an increased susceptibility to toxic substances produced in the course of a first infection. However, the *acquired* resistance to *B. muris* conferred by a first infection is not broken down

44. Lauda, E.: Bartonella, in Kolle, Kraus and Uhlenhuth: Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1930, vol. 8, no. 44, p. 1073.

45. Reitano, U.: Boll. Ist. sieroterap. milanese 9:325, 1930.

46. Ford, W. W., and Eliot, C. P.: Am. J. Hyg. 12:669, 1930.

by subsequent suprarenalectomy, though the *natural* resistance is markedly depressed.

In an effort to determine further the relation of the suprarenal gland to *acquired resistance*, the effect of suprarenalectomy in rats on the acquired immunity to typhoid vaccine, established by previous repeated injections of vaccine, was determined (Marmorston-Gottesman and Perla⁴⁷).

In a preliminary experiment the minimum lethal dose of a batch of typhoid vaccine for suprarenalectomized rats was determined. This was found to be 0.5 cc. Fourteen rats received three intraperitoneal injections of typhoid vaccine at weekly intervals (0.5 cc. and 1 cc.). Five days after the last injection these 14 rats, together with 10 normal rats, were suprarenalectomized. On the sixth day following the operation, 8 immunized suprarenalectomized rats were given intraperitoneally 5 cc. of typhoid vaccine, and 6, 1 cc. All the unimmunized rats were given twice the minimum lethal dose (1 cc.). Within twelve hours all the unimmunized rats died. Those rats that had been immunized and subsequently suprarenalectomized survived the injection of a quantity ten times the minimum lethal dose for suprarenalectomized rats.

Suprarenalectomy does not apparently diminish the acquired resistance to typhoid vaccine.

The striking difference in the effect of suprarenalectomy on acquired and natural resistance was demonstrated in infection with *B. muris*, with *T. lewisi* and with typhoid vaccine. Though suprarenalectomy markedly depressed the natural resistance of the rat to infection with *B. muris*, with *T. lewisi* and with typhoid vaccine, it did not influence the acquired resistance to these antigenic substances established by previous spontaneous or induced infection or by previous injection of the antigen. These observations indicate that once a cellular or a humoral immunity to an infection or an antigenic substance is established, this acquired resistance cannot be broken down by subsequent suprarenalectomy.

The depression in *natural resistance* that follows bilateral suprarenalectomy is a general phenomenon as is shown by the increased susceptibility to toxins and poisons and to bacterial and protozoan infections. It is probably a manifestation of a profound disturbance in cellular metabolism.

These studies strongly suggest that acquired resistance and natural resistance are dependent on different physiologic processes and are not merely quantitative variations of the same process as is generally assumed.

47. Marmorston-Gottesman, J., and Perla, David: Proc. Soc. Exper. Biol. & Med. 28:648, 1931.

Recently Steinbach studied the effect of suprarenalectomy on tuberculous infection in immature albino rats.⁴⁸ It is well known that the albino rat is highly resistant to the human and the bovine tubercle bacillus though it is readily infected with the avian strain.

Of 19 immature suprarenalectomized rats into which was injected 1 mg. of bovine tubercle bacillus B, 79 per cent showed definite evidences of tuberculosis in the abdominal organs but none in the lungs. No evidence of tuberculosis had been observed in 34 normal rats similarly inoculated, with a single exception. Of 18 suprarenalectomized rats inoculated with human tubercle bacilli on the fifth day after operation and killed after from four to sixty-five days, none showed evidence of tuberculosis, although acid-fast organisms could be demonstrated in all the tissues examined. Of 18 controls inoculated with 1 mg. of human tubercle bacilli (H 37), none showed evidences of tuberculosis. A small series of rats (4) received intraperitoneal injections of enormous doses of human tubercle bacilli (25, 50, 75 and 100 mg.). All 4 animals were killed in ninety days. The organs contained numerous bacilli, but no lesions were observed.

With a virulent avian strain, Steinbach observed that tuberculous lesions develop in 100 per cent of suprarenalectomized rats, but in only 50 per cent of normal controls.

From his studies, Steinbach concluded that bilateral suprarenalectomy lowers the natural resistance of albino rats to avian and bovine tuberculosis. The rat is normally highly refractory to infection with human and with bovine tubercle bacilli. Suprarenalectomy apparently does not affect the high natural resistance of the rat to human tubercle bacilli.

Perla and Marmorston, in an independent study (unpublished work) on the effect of suprarenalectomy on tuberculous infection in albino rats essentially confirmed these observations. However, they observed infections in suprarenalectomized rats with human tubercle bacilli as well.

Normal adult rats showed microscopic evidences of tuberculosis when given 1 mg. of bovine tubercle bacilli intraperitoneally within one month. Of 5 rats inoculated with 1 mg. of bovine tubercle bacilli C, a virulent strain, seven days after suprarenalectomy and killed thirty-one days later, 3 showed evidence of tuberculosis. Of 5 controls, only 1 showed evidence of tuberculosis in this interval. Of 5 suprarenalectomized rats inoculated with 1 mg. of human (P 15 B) tubercle bacilli B, seven days after operation and killed thirty-one days later, two showed evidence of tuberculosis in the abdominal organs and mediastinal nodes. In 3 controls tuberculosis did not develop. Of 4 suprarenalectomized adult rats into which was injected 1 mg. of avian tubercle bacilli (no. 112) all presented evidence of tuberculosis within one month. Of 4 controls, tuberculosis developed in 2 in the same period.

In adult rats suprarenalectomy increased the susceptibility to all three types of tubercle bacilli, avian, human and bovine.

48. Steinbach, M. M.: *Proc. Soc. Exper. Biol. & Med.* **27**:142, 1929.

Of interest is a second group of experiments in which the inoculated animals were killed after six months' observation. Thirteen rats were suprarenalectomized. Seven days later, 1 mg. of bovine tubercle bacilli C was injected into 8 of these and 5 mg. into the others. Five controls received 5 mg. of the same strain, and 8 controls, 10 mg. Six months later all were killed. Of the 5 controls that received 5 mg., 1 showed evidence of tuberculosis. Of the 8 controls that received 10 mg., 5 showed evidence of tuberculosis. Of the 8 suprarenalectomized rats into which 1 mg. was injected, none showed evidence of tuberculosis. Of the 5 suprarenalectomized rats given 5 mg., one showed evidence of tuberculosis. This experiment suggests that the tuberculosis which readily develops in suprarenalectomized rats one month following the injection of 1 mg. of bovine strain C apparently may heal without scarring and after six months no trace may be observed. The tuberculous lesions in the rat consist of groups of mononuclear phagocytes with little or no lymphocytic reaction. Some of these cells are fused to form giant cells with nuclei uniformly scattered, and they contain acid-fast organisms. Caseation and necrosis were observed only in tuberculosis produced by the avian strain.

IV. THE CORTICAL HORMONE AND NATURAL RESISTANCE

The mass of experimental evidence definitely establishes the significance of the suprarenal gland in the mechanism of *natural* resistance. It is important to determine whether the depression in resistance is associated with removal of the cortex or the medulla. It has been repeatedly shown that accessory chromaffin tissue exists in the body and that removal of the suprarenals does not destroy all this tissue.

Is the increased susceptibility of suprarenalectomized rats to toxins and infections, then, to be considered a manifestation of medullary or of cortical insufficiency, or of both? Three methods of approach have been used in an attempt to answer this question.

1. The effect of injections of the medullary secretion, epinephrine, on the resistance of suprarenalectomized rats to such poisons as histamine was studied by Wyman⁴⁹ and independently by Perla and Marmorston-Gottesman.⁵⁰ Wyman reported that he was able to protect suprarenalectomized rats against histamine poisoning by intraperitoneal injections of epinephrine.

As indicated in his data, 34 rats were treated with epinephrine. One group of 12 rats received three intraperitoneal injections of epinephrine prior to the injection of histamine. Of this group, 9 rats, or 75 per cent, survived. However, of 22 rats in a second group receiving a single intraperitoneal injection of epinephrine ten minutes prior to the injection of histamine, 3, or 13 per cent, survived. This is approximately the percentage of survival of untreated suprarenalectomized rats that received the same quantity of histamine. Wyman expressed the belief that the small amount of epinephrine present in the blood stream following its injection intraperitoneally is responsible for its protective action against the histamine

49. Wyman, L. C.: *Am. J. Physiol.* **87**:29, 1928.

50. Perla, David, and Marmorston-Gottesman, J.: *Am. J. Physiol.* **89**:152, 1929.

and is dependent on the immediate antagonistic effect of these two drugs. He maintains that the susceptibility to histamine poisoning of suprarenalectomized rats is due to insufficiency of the medulla and not of the cortex.

Perla and Marmorston-Gottesman⁵⁰ found that subcutaneous injections of epinephrine administered twice daily during seven days following suprarenalectomy afford protection to rats against a lethal dose of histamine in 50 per cent of cases. The last injection of epinephrine is administered two hours prior to the injections of histamine.

If the epinephrine is discontinued twenty-four hours before the injection of histamine its protective effect is markedly decreased. A single injection of epinephrine given two hours prior to the injection of histamine affords no protection to suprarenalectomized rats. The protective action of repeated subcutaneous injections of epinephrine against histamine poisoning in suprarenalectomized rats is in part due to a true hormonal effect and is not entirely dependent on the pharmacologic antagonistic action of epinephrine to histamine. It is probable that the medulla plays some part, if only a slight one, in the depressed resistance following suprarenalectomy.

2. Studies have been made on the effect of the presence of cortical rests, of removal of the cortex alone and of autoplasic cortical transplants on the resistance of suprarenalectomized rats. It has been our experience that even a small fragment of cortical tissue left in situ is sufficient to protect suprarenalectomized rats against injections of lethal doses of histamine. Kellaway and Cowell⁵¹ showed that if the cortex of both suprarenal glands of cats is destroyed but the medulla of one gland is left intact the animals show marked hypersensitivity to small doses of histamine. They maintained that deficiency of the cortex plays an important part in the susceptibility of suprarenalectomized animals to histamine. Wyman⁴⁹ was unable to observe protection against histamine in suprarenalectomized rats by autoplasic transplants of small fragments of cortical tissue. Jaffe and Plavska,⁵² continuing earlier observations on the susceptibility of suprarenalectomized rats to typhoid vaccine (Marine and Jaffe),¹⁹ noted that in the absence of accessory cortical tissue the sensitivity of rats to typhoid continued for as long as five months after operation. Suprarenalectomized rats that have a relatively high degree of resistance invariably possess gross cortical accessory tissue. In the absence of gross accessory tissue, autoplasic cortical transplants will protect suprarenalectomized rats against typhoid

51. Kellaway, C. H., and Cowell, S. J.: *J. Physiol.* **57**:82, 1922.

52. Jaffe, H. L., and Plavska, Alexandra: *Proc. Soc. Exper. Biol. & Med.* **23**:528, 1926.

vaccine in amounts otherwise lethal for suprarenalectomized rats. The evidence strongly suggests the greater significance of the cortex in the mechanism of resistance.

3. The discovery of the suprarenal cortical hormone by Hartman⁵³ and by Swingle and Pfiffner⁵⁴ afforded an opportunity to determine the effect of cortical hormone on the depressed resistance to toxins and infections in suprarenalectomized animals. These studies were made by Perla and Marmorston-Gottesman⁵⁵ and independently by Hartman and Scott.⁵⁶

The protective effect of an extract of the cortex of the suprarenal gland prepared by us according to the method of F. A. Hartman was determined with typhoid vaccine.^{55a} The cortical extract was administered intraperitoneally twice daily from the day of operation for a period of six days; the typhoid vaccine was then injected (1 cc. of extract was equivalent to 40 Gm. of cortex).

The minimum lethal dose of a batch of typhoid vaccine for suprarenalectomized rats was determined. The experimental animals were divided into four groups. One group of 17 rats received cortical extract twice daily from the day of operation to the end of the experiment. Of these, 4 rats on the sixth day were given 1 minimum lethal dose, 5, 2 minimum lethal doses, 4, 4 minimum lethal doses and 4, 6 minimum lethal doses of typhoid vaccine. A second group of 10 rats received equivalent amounts of salt solution. On the sixth day these were given 1 minimum lethal dose of typhoid vaccine. A third group of rats were untreated, and on the sixth day after operation these animals were given 1 minimum lethal dose of typhoid vaccine. A fourth group of 4 rats received cortical extract during only the twenty-four hour period before and after the injection of 1 minimum lethal dose of typhoid vaccine on the sixth day.

The rats that had been repeatedly inoculated with cortical extract survived as much as 4 minimum lethal doses of typhoid vaccine. The rats of the fourth group, which had received cortical extract only during the last twenty-four hour period, survived 1 minimum lethal dose of typhoid vaccine. The controls were killed by 1 minimum lethal dose of vaccine.

Independently Hartman and Scott⁵⁶ likewise observed the effect of cortical injections in raising the resistance of suprarenalectomized rats to typhoid vaccine. These experiments indicate that the cortical extract of Hartman raises the resistance of suprarenalectomized rats. It was suggested that a cortical extract may be biologically assayed by

53. Hartman, F. A.: *Endocrinology* **14**:229, 1930.

54. Swingle, W. W., and Pfiffner, J. J.: *Science* **71**:321, 1930.

55. (a) Perla, David, and Marmorston-Gottesman, J.: *Proc. Soc. Exper. Biol. & Med.* **28**:475, 1931; (b) **28**:650, 1931; (c) **28**:1022, 1931.

56. Hartman, F. A., and Scott, W. J. M.: *Proc. Soc. Exper. Biol. & Med.* **28**:478, 1931.

determining the minimal protecting amount to be administered within twenty-four hours before and after the injection of the minimal lethal dose of typhoid vaccine for suprarenalectomized adult rats on the sixth day after suprarenalectomy.

In subsequent experiments the effect of injections of cortin on the resistance of suprarenalectomized rats to histamine was studied.⁵⁷

Adult suprarenalectomized rats are killed by from 100 to 120 mg. of histamine per kilogram of body weight administered on the sixth day after operation. Normal rats survive from 700 to 900 mg. per kilogram. For 6 week old suprarenalectomized rats the minimum lethal dose of histamine is from 150 to 200 mg. per kilogram. Fourteen suprarenalectomized rats received injections of 0.5 cc. of cortin twice daily (1 cc. = 40 Gm. of cortex). On the sixth day, 6 rats received 150 mg. of histamine per kilogram, 3, 200 mg.; 3, 300 mg., and 2, 500 mg. All survived.

The daily injections of cortin raised the resistance to at least 3 minimum lethal doses of histamine. The maximal amount of histamine that suprarenalectomized rats treated with cortin will survive was later determined and it was observed that the resistance of suprarenalectomized rats could be raised almost to the normal level^{55c} when 2 cc. of cortin (equivalent to 80 Gm. of cortex) was administered daily during the first two weeks following operation.

Five rats thus treated were given 600 mg. of histamine per kilogram on the sixth day. All survived. Three were given 700 mg. of histamine per kilogram, and of these, 2 survived. Of 8 given 800 mg. per kilogram, 3 survived. Of 3 controls given 900 mg. per kilogram, 2 survived, and of 3 controls given 950 mg. per kilogram, 1 survived.

From these results it is apparent that it is possible in many instances to raise the resistance of suprarenalectomized rats almost to the level of the resistance of normal rats by repeated injections of large amounts of cortin. The effect of the cortical hormone is specific. Previous work had shown that large amounts of saline solution have no demonstrable effect on the resistance of suprarenalectomized rats. Repeated injections of epinephrine have only a slight effect.

An extract of the spleen made in the exact manner as the cortical extract failed to produce any increase in the resistance of suprarenalectomized rats. The anterior pituitary hormone of Doisy (theelin) did not raise the resistance of suprarenalectomized rats. With the male sex hormone (Funk and Harrow) negative results were obtained.

We believe, therefore, that the action of cortin on the resistance of suprarenalectomized rats to histamine and other toxins and poisons is

57. Perla and Marmorston-Gottesman (footnote 55 *b* and *c*).

a measure of the specific activity of the life-prolonging hormone of the suprarenal cortex.⁵⁸

It is evident that the marked susceptibility of suprarenalectomized rats to histamine poisoning is not due to insufficiency of epinephrine, or is so only in part, as maintained by Wyman, but is primarily the result of cortical insufficiency.

The decrease in natural resistance that follows suprarenalectomy in animals is due primarily to *cortical insufficiency*, and repeated injections of the cortical hormone increase the resistance of the suprarenal-ectomized animal.

The discovery of a cortical hormone and the demonstration that it raises the resistance of rats with suprarenal insufficiency suggest further research in the therapeutic use of cortical extracts in the treatment of human infectious disease. In many infectious diseases and in severe burns and intoxications the cortex is markedly injured. It is probable that injections of the cortical hormone may prove of great value in such conditions. Few studies of this nature have been made. Whitehead and Smith⁵⁹ used injections of cortical extract (Swingle and Pfiffner⁵⁴) in the treatment of patients with severe infections with somewhat encouraging results.

Five patients were treated. In the first patient, who was suffering from typhoid fever, 2 cc. of the extract (equivalent to 100 Gm. of cortex) was given on the eleventh day. The temperature became normal on the second day and remained so during the next fourteen days. The second patient, with undulant fever of six weeks' duration, was given several injections, and the temperature returned to normal within two days. The third patient, who had postoperative erysipelas, was unsuccessfully treated. He died after temporary improvement. The fourth patient, who had lymphangitis of the hand with resultant sepsis, was cured after one injection of 2 cc. of cortical hormone. In the fifth patient, a virulent ethmoid sinus infection cleared after several injections of extract. This patient remained under observation for one month.

58. It was suggested that the protective action of cortical extracts against histamine poisoning in suprarenalectomized rats provides a better means of biologically assaying the potency of such extracts than does typhoid vaccine, which was previously suggested. Histamine is a standard chemical that varies little in toxicity. The amount of cortical extract (injected intraperitoneally into suprarenalectomized albino rats on the fifth and sixth days after operation) necessary to protect these rats against 200 mg. of histamine per kilogram of body weight may be considered as a standard unit. DeMeio and Lewis (Compt. rend. Soc. de biol. **111**:822, 1932) confirmed these observations on the effect of cortical extracts on the resistance of suprarenalectomized rats to poisons. Repeated injections of the cortical extract of Swingle and Pfiffner⁵⁴ increased the resistance of suprarenal-ectomized rats to morphine hydrochloride. These authors suggested assaying cortical extracts by this method.

59. Whitehead, R. W., and Smith, C.: Proc. Soc. Exper. Biol. & Med. **29**: 672, 1932.

These instances are too few to be of value in determining the use of cortin in infections, but were reported only as the results of a preliminary investigation. A wide trial of cortin therapeutically is imperative, but at present the cost of extraction is prohibitive. A method of obtaining larger yields more simply must be discovered before this important hormone may be available for general use.

V. SIGNIFICANCE OF THE DEPRESSION IN NATURAL RESISTANCE FOLLOWING SUPRARENALECTOMY

The depression in natural resistance following suprarenalectomy in animals is a general phenomenon, not specific for any one type of intoxication. It was believed previously that the suprarenals possess the capacity for direct detoxification of poisons somewhat as the liver does. The evidence for this hypothesis was gathered from the pathologic changes which usually occur in the cortex of the suprarenals in acute and chronic infections, in acute intoxications and in severe burns. It was, further, well established that suprarenalectomized cats, dogs and rats are extremely susceptible to spontaneous infections of the respiratory tract. The detoxification theory, however, has been discarded, since it was found contrary to the observations of many investigators. Marine³ and others found no diminution in the toxicity of diphtheria toxin when it was mixed in vitro with emulsions of suprarenal cortex.

The general character of the diminution in resistance that follows suprarenalectomy in animals suggests that it may be a manifestation of an interference with the normal cellular metabolism which occurs with suprarenal cortical insufficiency. When this disturbance is relieved by the administration of the life-prolonging hormone of the cortex the natural resistance of the animal may be raised.

A brief consideration of certain phases of the physiology of the suprarenal cortex, while not directly pertinent to this review, may aid in understanding the relation of the mechanism of resistance to cortical function.⁶⁰ The studies of the past decade on the physiology of the suprarenal cortex have revealed its fundamental importance in the maintenance of life.

Repeated injections of the cortical hormone, isolated independently by Hartman⁵³ and by Swingle and Pfiffner,⁵⁴ prolong the lives of suprarenalectomized cats and dogs and of patients suffering with Addison's disease.⁶¹ The nature of this controlling mechanism is still obscure.

60. For a review of the literature on the physiology and pathology of the suprarenal glands, the reader is referred to the recent monographs by Jaffe (*Arch. Path.* **3**:414, 1927), Britton (*Physiol. Rev.* **10**:617, 1930) and Hartman, Brownell and Lockwood (*Endocrinology* **16**:521, 1932).

61. Hartman, F. A.; Aaron, A. H., and Culp, J. E.: *Endocrinology* **14**:438, 1930. Rowntree, L. G.; Greene, C. H.; Ball, R. G.; Swingle, W. W., and Pfiffner, J. J.: *J. A. M. A.* **97**:1446, 1931.

There is, however, considerable evidence of the relation of the cortex to metabolism. In earlier work, Marine and his co-workers^{62a} observed that the metabolic rate of infants shows a striking increase at the time the suprarenal cortex undergoes involutional changes. At this period there is also rapid growth of the thymus and lymph glands. Marine suggested a causal relation between this normal suprarenal involution in infants and the increased heat production and lymphoid hyperplasia, particularly in view of the fact that both increased heat production and lymphoid hyperplasia may be produced in animals by sublethal injury of the cortex. The influence of the cortex in metabolism and the relation of the cortical function to disturbances of the thyroid gland and to exophthalmic goiter have been established in an extended series of experiments by Marine and his co-workers.⁶² The metabolism of completely suprarenalectomized cats can be maintained by injections of the cortical hormone, according to Hartman, Griffith and Hartman⁶³ and Swingle, Pfiffner and Webster.⁶⁴

The rôle of suprarenal cortex as a regulatory mechanism in the maintenance of normal conditions of temperature and muscle tone has been emphasized by Hartman and his associates,⁶⁵ Rogoff and Stewart⁶⁶ and others. Suprarenalectomized animals and patients with Addison's disease show a lowered resistance to cold. Exposure to low temperatures precipitates acute insufficiency. Suprarenalectomized rats are unable to withstand high temperatures.⁶⁷ The outstanding importance of the suprarenal tissues in the chemical regulation of body temperature was also recently emphasized and reviewed by Cannon.⁶⁸

62. (a) Marine, David; Lowe, B. H., and Cipra, Anna: *J. Metab. Research* **2**: 329, 1929. (b) Marine, David, and Baumann, E. J.: *ibid.* **1**:1, 1922. (c) Marine, David; Baumann, E. J., and Cipra, Anna: *ibid.* **72**:248, 1925. (d) Marine, David: *Arch. Path.* **1**:175, 1926; (e) *Am. J. M. Sc.* **180**:767, 1930. (f) Marine, David; Baumann, E. J., and Webster, Bruce: *Proc. Soc. Exper. Biol. & Med.* **28**:327, 1931. (g) Marine, David, and Baumann, E. J.: *Am. J. Physiol.* **57**:135, 1921; (h) **59**:353, 1922. (i) Shapiro, S., and Marine, David: *Endocrinology* **5**:699, 1921.

63. Hartman, F. A.; Griffith, F. R., and Hartman, W. E.: *Am. J. Physiol.* **86**:360, 1928.

64. Swingle, W. W.; Pfiffner, J. J., and Webster, Bruce: *Proc. Soc. Exper. Biol. & Med.* **28**:728, 1931. Webster, Bruce; Pfiffner, J. J., and Swingle, W. W.: *Am. J. Physiol.* **99**:710, 1932.

65. Hartman, F. A.; Brownell, K. A., and Crosby, A. A.: *Am. J. Physiol.* **98**:674, 1931.

66. Rogoff, J. M., and Stewart, G. N.: *Am. J. Physiol.* **86**:20, 1928.

67. Hartman, F. A.; Brownell, H. A., and Lockwood, J. E.: *Endocrinology* **16**:521, 1932.

68. Cannon, W. B.: *Ergebn. d. Physiol.* **27**:380, 1928.

The influence of the suprarenals on carbohydrate metabolism is primarily attributable to medullary function (Cori and Cori⁶⁹), but the recent studies of Britton⁷⁰ indicate that in severe suprarenal cortical insufficiency of cats a low blood sugar content occurs. The concentration of the blood sugar can be raised to normal by the administration of an adequate amount of cortin (Hartman⁶⁷).

The occurrence of a lipid nephrosis in suprarenalectomized cats was described by Marine.⁷¹ Marshall and Davis⁷² demonstrated a steady rise in the nonprotein nitrogen of the blood in bilaterally suprarenalectomized cats. The rise in blood nitrogen is probably a terminal manifestation of a severe general disturbance in metabolism.

That the suprarenal glands are not intimately associated with cholesterol metabolism, as was believed by earlier investigators (Aschoff⁵), was demonstrated by the studies of Baumann and Holly.⁷³ They found no change in the blood cholesterol in suprarenalectomized rabbits except as a terminal phenomenon. The lipid phosphorus and cholesterol show a sharp rise during the last days of life of the suprarenalectomized animal. This work has since been confirmed by Randles and Knudson⁷⁴ and by Lucas.⁷⁵

Recent work indicates a close relationship between cortical function and cellular oxidation. In studying oxidation systems in plant life, Szent-Györgyi⁷⁶ succeeded in isolating a hexuronic acid from cabbage and other plants. He found large amounts of this strong reducing substance in the suprarenal cortex of animals, but in no other tissues does it occur in appreciable amounts.⁷⁷ From the chemical properties of this compound it is important, apparently, in oxidation-reduction systems in cellular metabolism. Independently Szent-Györgyi⁷⁷ and Waugh and King⁷⁸ identified hexuronic acid with the antiscorbutic vitamin C, and King isolated the same compound from orange and lemon juice concentrates. This work opens a new field in the physiology of the suprarenal cortex in relation to the utilization of vitamin C and the importance of the cortex in certain types of anaerobic oxidation-reduction systems in

69. Cori, Carl F., and Cori, G. T.: *J. Biol. Chem.* **79**:309, 321 and 343, 1928.

70. Britton, S. W., and Silvette, H.: *Am. J. Physiol.* **99**:15, 1931.

71. Marine, David: *Arch. Path.* **6**:169, 1928.

72. Marshall, E. K., and Davis, D. M.: *J. Pharmacol. & Exper. Therap.* **8**:525, 1916.

73. Baumann, E. J., and Holly, O. M.: *J. Biol. Chem.* **55**:457, 1923.

74. Randles, F. S., and Knudson, Arthur: *J. Biol. Chem.* **67**:xvii, 1926.

75. Lucas, G. H. W.: *Am. J. Physiol.* **77**:114, 1926.

76. Szent-Györgyi, Albert: *Biochem. J.* **22**:1387, 1928.

77. Szent-Györgyi, Albert: *Science* **72**:125, 1930. Svirbely, J. L., and Szent-Györgyi, Albert: *Biochem. J.* **26**:865, 1932.

78. Waugh, W. A., and King, C. G.: *Science* **76**:630, 1932; *J. Biol. Chem.* **97**:325, 1932.

the body. (Hexuronic acid is not identical with the "life-prolonging" hormone of the suprarenal cortex.)

From this brief consideration of the physiologic action of the cortex it is apparent that the fundamental relation of the cortex to general metabolism and particularly to cellular metabolism is strongly suggested by the experimental work of many investigators.

It is the opinion of investigators in this field that the lowering of resistance is the result of an injury to all the body cells. In a recent review on this subject Marine³ expressed the opinion that this injury is brought about by the loss or absence of some nutritional factor normally supplied by the cortex, which permits the cells of the body to be more readily attacked by various poisons.

It would seem probable that the mechanism of natural resistance is dependent on the maintenance of normal cellular metabolism and that procedures that impair oxidation and reduction processes depress the resistance of the somatic cells to all abnormal stimuli, whether marked variations in temperature or poisons, toxins or infectious agents. When the physiologic action of the cortical hormone is better understood, the chemical nature of the life-prolonging hormone identified and its relation to oxidation-reduction systems and hexuronic acid determined, a new approach to the problem of the mechanism of natural resistance in the body may be available. Natural resistance is intimately bound up with the chemistry of cellular metabolism.

SUMMARY

Removal of the suprarenal glands in rats is followed by a disturbance in the formation of antibodies, most marked during the second week after operation. The depression in antibody formation is dependent on a disturbance of the water exchange in the tissues, and restoration of a normal water exchange by the administration of large quantities of fluid containing isotonic amounts of sodium salts restores the antibody-forming capacity to normal.

The suprarenal glands are important in the maintenance of the natural resistance of the body to intoxications, poisons and bacterial and protozoan infections.

While the natural resistance of the suprarenalectomized animal is markedly depressed, the acquired resistance, produced by a previous injection of antigen or by previous infection, is unaffected.

The depression in natural resistance following suprarenal insufficiency is probably dependent on loss of cortical function, since injections of the cortical hormone raise the resistance of suprarenalectomized animals. It is hypothesized that the depression in natural resistance is dependent on a disturbance of the general cellular metabolism, possibly of the oxidation-reduction systems.

Notes and News

University News, Promotions, Registrations, Appointments, Deaths, etc.

—According to *Science* Robert Allan Moore, instructor in pathology in the Western Reserve University and assistant pathologist to Lakeside Hospital, Cleveland, has been appointed assistant professor of pathology in the Cornell University Medical College, New York.

Walter G. Sackett, bacteriologist at the Colorado Experiment Station at Fort Collins since 1908, has resigned.

John J. Phair, bacteriologist of the Cincinnati Department of Health, has been appointed to the staff of the International Health Division of the Rockefeller Foundation for work on undulant fever at Montpellier, France.

At the recent meeting of the National Tuberculosis Association in Toronto the Trudeau Medal was awarded to Lawrason Brown of the Trudeau Sanatorium, Saranac Lake, New York.

George R. Minot, of the Harvard Medical School and director of the Thorndike Memorial Laboratory in the Boston City Hospital, has been awarded the Moxon Gold Medal of the Royal College of Physicians, London, for his work on the treatment of pernicious anemia with liver.

Alan R. Moritz has been promoted to associate professor of pathology in the Western Reserve University, Cleveland.

Georges Joannovic, pathologist and founder of the Yugoslav Faculty of Medicine in Belgrade, Serbia, has died at the age of 62.

Society News.—On May 10, 1933, the American Association of Neuropathologists was established in Washington with Arthur Weil of Chicago as president and A. Ferraro of New York as secretary-treasurer.

DOCTORATES IN BACTERIOLOGY AND ANIMAL PATHOLOGY GRANTED BY AMERICAN UNIVERSITIES, 1932-1933

Clarence J. West and Callie Hull, Research Information Service,
National Research Council, Washington, D. C.

BACTERIOLOGY

Chicago: Jorgen Maurice Birkeland, "Serological Studies of Plant Viruses." Mary Estill Caldwell, "Studies on Dissociation of Certain Paratyphoid Bacilli: The Role of Variants in the Precipitation of Calcium Sulphite." Robert Barton Dienst, "Studies on the Variation of *Bacterium Dysenteriae* (Sonne)."

Columbia: James Thomas Culbertson, "A Quantitative Study of the Precipitin Reaction with Special Reference to Crystalline Egg Albumin and Its Antibody." Sidney J. Klein, "The Lysis of *Pneumococcus* by Saponin; Sensitizing Action of Sterols." Hildrus Augustus Poindexter, "Defense Mechanism in *Trypanosoma Equiperdum* and *Trypanosoma Lewisi* Infections in Guinea-Pigs and Rats." Florence Mercedes Stoné, "Porphyrin Compounds Derived from Bacteria."

Cornell: Dorsey William Bruner, "The Influence of Nutritive Conditions on Acid-Fastness of Bacteria." Fred Douglas Patterson, "Avian Coccidiosis: A Study of Some of the Factors Concerned in Its Control."

Illinois: Francis Matthew Clark, "The Formation of Hydrogen Sulfide by Thermophilic Bacteria." John B. Rehm, "The Effect of Aeration on Micro-Organisms." Elbert Hollis Ruyle, "The Microbiology of Canned Meat Products." Isaac Evan Wheaton, "The Effect of Salt on Micro-Organisms."

Iowa State College: Mervyn Avery Collins, "The Action of Lipolytic Bacteria on Some Simple Tri-Glycerides and Some Natural Fats." Arthur Cecil Fay, "The Effect of Hypertonic Sugar Solutions on the Thermal Resistance of Bacteria." William Hillman Willis, "The Metabolism of Some Nitrogen-Fixing Clostridia."

Johns Hopkins: Andrés Rodríguez, "The Survival of Members of the *Bacillus Coli-Lactis Aerogenes* Group in Milk Pasteurized in the Laboratory and in the Commercial Plants, with Observations on the Resistance of *Bacillus Coli* to a Temperature of 142 F."

Kansas: Mary Elizabeth Elmore, "A Further Study of the Antigenic Properties of *Euglena Gracilis*, Klebs, with Related Phenomena." Paul W. Kabler, "Studies in Anaphylaxis."

Michigan: Ardzoony Arthur Packchianian, "Experimental Trypanosoma Brucei Infection and Immunity in Various Species of Animals; Blood Chemistry and Electrical Conductivity of Nagana Blood."

Minnesota: William Richard Carroll, "A Study of *Rhizobium* Species in Relation to Nodule Formation on the Roots of Florida Legumes." Ernest Oliver Herreid, "The Microbiology of Cheeselike Flavors in Unsalted Butter."

New York: Dorothy Behner Holmes, "Studies in the Virulence and Colony Variability of Tubercle Bacilli Developed Under Different Conditions with Especial Reference to the *Bacillus Calmette-Guérin*."

Northwestern: Arnold Gerhard Wedum, "Investigation of Certain Synthetic Glucosides for Antigenic Properties."

Ohio State: Ruth Ella Moore, "I. Studies on Dissociation of *Mycobacterium Tuberculosis*: II. A New Method of Concentration of the Tubercle Bacilli as Applied to Sputum and Urine Examination."

Pennsylvania: Albert Dickman, "Studies on the Waxmoth, *Galleria Mellonella*, with Particular Reference to the Digestion of Wax by the Larvae."

Rochester: Ralph Porter Tittsler, "The Electrophoresis of *Escherichia Coli* Grown on Culture Media of Varied Composition."

Rutgers: Ernest Rudolph Purvis, "A Study of Microbiological Population of Peat and Its Role in the Chemical Processes of Peat Formation."

Virginia: Leland Edson Starr, "Undulant Fever and Its Relation to Brucellosis in Cattle and Swine in Virginia."

Wisconsin: Lawrence Wayneworth Brown, "The Relation of the Oxidation-Reduction Character of Sterile Bacteriological Media to the Growth of Aerobic Organisms." Janet Ruth McCarter, "The Bacteriology of Certain Species of Micro-Organisms, Both Those Belonging in and Those Related to the Genus *Mycobacterium*." Marion Henrietta Thauer, "Certain Factors Affecting the Reduction of Methylene Blue in Milk."

Yale: George Dexter Brigham, "A Systematic Study of the *Pasteurella* Genus." Ruth Cameron, "A Search for a Specific Toxin in *Salmonella Aertrycke* (Var. *Meleagridis*)." Stanley Eugene Hartsell, "The Taxonomy of *Clostridium Putrificum* and Its Establishment as a Definite Entity: *Clostridium Lentoputrescens*, Nov. Spec." James Ewing Weiss, "*Lactobacillus Bifidus* Tissier and Its Biological Position in the Group of Aciduric Organisms."

ANIMAL PATHOLOGY

Johns Hopkins: John Holmes Dingle, "Bacterial Carbohydrates: Their Isolation, Serological Specificity and Immunological Significance." Aurel Overton Foster, "Studies on the Resistance of Dogs and Cats to Infection with the Dog Hookworm, *Ankylostoma Canium*." Vernal Irons, "Studies on Bird-Pox (*Epithelioma Contagiosum*)." Sydney Raffel, "Specific and Nonspecific Immunity in *Trypanosoma Equiperdum* Infections." Mary Shaw Shorb, "Heterophile Antigen in Bacteria."

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

EXPERIMENTAL FAT EMBOLISM OF THE HEART. S. A. SZUREK and Z. G. CZAJA, *Am. J. Path.* **9**:47, 1933.

From 1 to 2 cc. of oil squeezed from the omental and subcutaneous fat of normal dogs was injected into the descending branches of the anterior coronary artery of dogs. The heart was examined at various subsequent periods for thirty days. In limited portions of the myocardium blocking of all the capillaries with oil appeared to be followed by infarction rather than by the occlusion of the arterial branches which occurs in ordinary coronary thrombosis and embolism. Muscular fibers adjacent to oil infarcts were fatty at times, but it could not be decided whether the fat in such fibers was embolic in origin and had accumulated in the fiber after passing through the capillary wall. It is concluded that fat embolism should be considered as a possible cause of minute scars scattered through the myocardium.

THE EFFECTS OF POTASSIUM BICHROMATE ON THE MONKEY'S KIDNEY. W. C. HUNTER and J. M. ROBERTS, *Am. J. Path.* **9**:133, 1933.

Potassium bichromate in dosages employed in experiments performed on monkeys affects diffusely the proximal and distal convoluted tubules and glomeruli of the kidney. The type of injury is comparable to that induced by uranium nitrate and mild mercurous chloride. The drug is locally corrosive when administered subcutaneously, and the quantity absorbed varies considerably in different animals of the same species. Definitely chronic renal lesions were obtained in but one animal of six. Following repeated injections of potassium bichromate there occurs a regeneration of tubular epithelium of distinctly atypical morphology which is resistant to further injury by the nephrotoxin.

AUTHORS' SUMMARY.

MYCOSIS FUNGOIDES IN MOTHER AND IN DAUGHTER. OLIN J. CAMERON, *Arch. Dermat. & Syph.* **27**:232, 1933.

A woman, aged 45, had mycosis fungoides which resulted fatally four years later. Five years after her death her daughter, aged 28, presented the typical picture of mycosis fungoides. This is the first instance of mycosis fungoides reported in two members of the same family, although the familial occurrence of leukemia and of Hodgkin's disease has been reported.

S. W. BECKER.

SIMMONDS' DISEASE (CACHEXIA HYPOPHYSEOPRIVA). SOLOMON SILVER, *Arch. Int. Med.* **51**:175, 1933.

Simmonds' disease may be defined as a clinical state, occurring most commonly in women and characterized by progressive, extreme emaciation, premature aging, wrinkling of the facial skin, loss of pubic and axillary hair, dental caries and loss of libido and sexual function, accompanied by a depression of the basal metabolic rate and, often, by mental disturbances closely simulating Korsakoff's syndrome. In addition to advanced obvious cases, attention is called to the mild, abortive forms that masquerade under such diagnoses as arteriosclerotic cachexia, syphilitic cachexia and latent tuberculosis. The pathologic basis for the condition is varied, but in general may be stated as any process resulting in the destruction of the anterior lobe of the pituitary gland. The only constant postmortem observation is an abnormal smallness of the viscera, which was first pointed out by Simmonds. Since it is now established that acromegaly depends on the hyper-

activity of the eosinophilic elements, it is perhaps not unlikely that Simmonds' disease has as its physiologic basis a hypofunction of these cells. At least one might expect something of this nature from the directly opposite clinical pictures presented by acromegaly and by Simmonds' disease. It is noted, however, that extensive, almost complete destruction can take place without evidence of characteristic symptoms.

IRVING B. GOLD.

INFLUENCE OF THE PITUITARY GLAND ON ERYTHROCYTE FORMATION. R. C. MOEHLIG and G. S. BATES, *Arch. Int. Med.* **51**:207, 1933.

Two cases of polycythemia vera with pituitary basophilism, which came to autopsy, are described. One was a case of primary basophilic adenoma giving rise to the syndrome recently described by Cushing. The other was a case of secondary basophilism in response to a suprarenal tumor. The occurrence of polycythemia experimentally induced in dogs by bilateral adrenalectomy is also reported. In these animals rapid and marked hyperplastic changes of the pituitary cells were found. The hyperplasia was, in the majority of cases, confined to the basophil cells. The pituitary secretion has an important influence on erythrocyte formation. Primary disease of the suprarenal cortex results in secondary pituitary changes, and this accounts for many signs and symptoms erroneously ascribed to the suprarenal cortex. The specific and selective embryohormonic relations of the pituitary gland to mesodermal tissues offer a reasonable explanation for the polymorphic signs and symptoms of pituitary disturbances.

AUTHORS' SUMMARY.

ACIDS AND OTHER SUBSTANCES IN THE PRODUCTION OF GASTRIC ULCERS. J. FRIEDENWALD, M. FELDMAN and S. MORRISON, *J. Exper. Med.* **57**:203, 1933.

The various substances utilized in these experiments, when injected into the muscular coat of the wall of the stomach, did not have any significant relationship to the production of ulcer. Weak solutions of hydrochloric acid had no corrosive effect on the gastric mucosa and rarely produced ulceration. Stronger solutions produced definite ulcerations. No relationship could be demonstrated between the injection of various substances into the stomach wall and the production of hyperacidity. The prolonged use of histamine administered subcutaneously was not a factor in the production of chronic ulcers, even after a 1 per cent solution of hydrochloric acid was injected into the muscular coat of the stomach.

AUTHORS' SUMMARY.

EFFECTS OF ANTERIOR PITUITARY EXTRACTS ON METABOLISM. O. H. GAEBLER, *J. Exper. Med.* **57**:349, 1933.

Solutions of the globulin fraction of alkaline extracts of the anterior lobe of beef pituitary glands, when administered intraperitoneally or subcutaneously to dogs for one or two days, greatly increase the nitrogen balance. The nitrogen content of the urine falls markedly and the nonprotein nitrogen of the blood decreases, while the nitrogen of the feces remains the same. The nitrogen gained may be either retained or lost, indicating that it may be converted into reserve protein rather than into permanent structures. Sudden gains in weight which follow the injections are always followed by losses in weight. The effect of the extracts on protein catabolism is greatest when the latter is high, as in adult dogs having either a negligible positive nitrogen balance or a negative nitrogen balance, while consuming a diet high in protein and adequate in calories. Both the fall and the subsequent rise in the excretion of nitrogen are due to changes in the excretion of urea. Other results of the brief treatments are: great increase in the intake of water and in the volume of urine, marked thirst, a slight rise in temperature and a remarkable increase in heat production effected by the oxidation of fat. Mature female dogs were used, and in one of these lactation occurred after some of the injections.

AUTHOR'S SUMMARY.

NUTRITIONAL ENCEPHALOMALACIA IN CHICKS. A. M. PAPPENHEIMER and M. GOETTSCH, *J. Exper. Med.* **57**:365, 1933.

Nutritional encephalomalacia may be induced in chicks up to the age of approximately 2 months. As the number of preliminary feeding periods of a natural diet is increased, the percentage incidence of the disease becomes progressively less. The average time between the institution of the diet and the appearance of the disease tends to diminish. There is no correlation between growth and incidence of the disease. Various breeds are equally susceptible.

AUTHORS' SUMMARY.

EFFECT OF E AVITAMINOSIS ON THE INTERSTITIAL CELLS OF THE TESTIS. A. JUHÁSZ-SCHÄFFER, *Virchows Arch. f. path. Anat.* **286**:834, 1932.

Opinions as to the function of the interstitial cells of the testis have been based to a large degree on procedures that lead to atrophy and disappearance of the tubular epithelium. More recent opinion tends to the conclusion that the increase in interstitial tissue that follows such procedures is apparent rather than real. In a previous communication the author described the effects of a deficiency of vitamin E on the testis of young rats. Spermatogenesis ceases, the seminal tubular epithelium degenerates and disappears, and the testis becomes atrophic. The interstitial tissue not only is unchanged but appears relatively more prominent than normal. The aim of the present investigation was to determine whether any actual changes in the amount of the interstitial tissue occur. Planimetric methods of determining the relative volumes of interstitial tissue and tubular tissue in relation to the entire testis proved unsatisfactory. The method finally selected was the counting of the nuclei of the interstitial cells of the testes of rats on a diet deficient in vitamin E and of their normal litter mate controls. No significant change in the number of interstitial cells could be detected. Similar negative results were obtained when a unilateral castration was done before the rats were placed on the deficient diet. During the period of recovery from the changes induced by the deficient diet, in which regeneration of the tubular epithelium occurs, no changes in the number of interstitial cells were noted.

O. T. SCHULTZ.

ALCOHOL AND CIRRHOSIS OF THE LIVER. RUDOLPH SIVO, ELEMER EGEDY and JOSEF ERDOS, *Ztschr. f. d. ges. exper. Med.* **84**:459, 1932.

In healthy persons the albumin-globulin ratio varies between 3.0 and 5.5, the average being 3.9. The globulin value varies from 15 to 24 per cent. This ratio remains constant under all sorts of physiologic conditions of the organism. In cirrhosis of the liver there is a significant increase in globulin at the expense of the albumin, the albumin-globulin ratio averaging 0.96 and ranging from 1.8 to 0.49, but the diagnosis of hepatic cirrhosis cannot be determined on this basis alone. In alcoholic patients who do not have cirrhosis of the liver the albumin-globulin ratio is around 2.01, and this increase in globulin denotes a disposition to cirrhosis. In animal and human experiments occasional ingestion of alcohol leads to a temporary increase in globulin, and with the persistent use of this substance the globulin increase becomes established. Tuberculosis and syphilis of long duration also lead to an increase in globulin as do other factors concerned in the etiology of cirrhosis of the liver.

AUTHORS' SUMMARY.

THE ORIGIN OF CREATINE AND THE TREATMENT OF PROGRESSIVE MUSCULAR ATROPHIES WITH GLYCINE. KARL THOMAS, ADE T. MILHORAT and FRITZ TECHNER, *Ztschr. f. physiol. Chem.* **205**:93, 1932.

Patients with progressive muscular atrophy were fed glycine, and an increased creatinuria was observed, which gradually decreased and sometimes reached values below those present before the onset of treatment. During the stage of hypercreatinuria the patients complained of pain and an itching sensation in the muscles, especially the last affected ones. These symptoms disappeared gradually with the

decrease of the creatine excretion. The patients felt less tired and were able to use their muscles. The improvement lasted for about one month after discontinuation of the treatment. Patients with secondary muscular atrophy (amyotrophic lateral sclerosis, rheumatic arthritis, congenital idiocy) did not respond to treatment with glycine. It is asserted that the administration of glycine represents a causative therapy in progressive muscular atrophy.

WILHELM C. HUEPER.

Pathologic Anatomy

CEREBRAL ANEURYSMS AS SOURCES OF APOPLECTIC HEMORRHAGES. H. BEITZKE, *Beitr. z. path. Anat. u. z. allg. Path.* **87**:272, 1931.

Twelve cases of cerebral hemorrhage were studied for aneurysms by serial sections, and aneurysms were found in seven. The aneurysms were small (from the size of a grain of sand to that of a millet seed). In six cases the histologic picture was that of atherosclerosis (termed angionecrosis by some authors). There is considered to be a primary focal medial injury. If this is gradual, dilatation and compensatory intimal thickening occur; if it is acute, necrosis or calcification of the media occurs, there is no compensatory internal change, and an aneurysm forms rapidly. Syphilis was found in one case.

The author believes cerebral aneurysms more frequent in the pathogenesis of hemorrhage than reports would indicate. The cause of the medial injury he regards as either sclerosis or syphilis. The rupture is produced by sudden rises in tension. The occurrence of a huge hemorrhage as the result of the conglomeration of multiple small hemorrhages is considered rare.

W. S. BOIKAN.

SILICOSIS OF THE SPLEEN. A. EDINGER, *Centralbl. f. allg. Path. u. path. Anat.* **55**:1, 1932.

A firm spleen, 17 by 9.5 by 3.5 cm., containing many nodules and firm yellow streaks in the pulp, was found in the body of a 36 year old woman who had suffered from chronic mitral endocarditis and glomerular nephritis and who died of uremia. The nodules consisted of concentric layers of connective tissue in the wall of thickened blood vessels and in the smaller trabeculae. Similar nodules occurred in the lung parenchyma, in the walls of the bronchi and pulmonary vessels, in the lymph glands of the hili of the lung and spleen and in the posterior mediastinum. In the nodules quartz dust was found, although in all of them it appeared that silicon dioxide had induced a connective tissue reaction much greater than that occasioned by the infiltration of dust alone. Edinger believes that the transport of silicates may have occurred either through the blood stream after intravasation in the pulmonary lymph glands or in a retrograde fashion through the lymph channels into the spleen.

GEORGE RUKSTINAT.

RELATION BETWEEN THE SIZE AND WEIGHT OF THE SPLEEN. E. VON GIERKE, *Centralbl. f. allg. Path. u. path. Anat.* **55**:129, 1932.

The author believes that a rather accurate idea of the weight of the spleen can be obtained by expressing as weight in grams one-half the product of the length, breadth and thickness in centimeters. He cites examples in which exact weights and measurements seem roughly to substantiate his ideas.

GEORGE RUKSTINAT.

UNUSUAL LIPOMATOSIS OF THE PANCREAS. O. MICHAELIS, *Centralbl. f. allg. Path. u. path. Anat.* **55**:131, 1932.

The pancreas was so large that it could be palpated through the abdominal wall and was thought to be a malignant tumor. A large, knobbed, fist-sized portion of the organ reached the hilus of the liver, surrounded the vessels here and compressed the portal vein and cisterna chyli. The tail of the tumor was the size of

a child's arm, and was intimately connected with the surrounding tissues. A chylous ascites of 3.5 liters existed. The fat in the pancreas was predominantly cholesterol, and in it small and large clumps of pancreas were visible microscopically. The origin of this huge fatty deposit apparently lay in the lipid nephrosis from which the patient had suffered.

GEORGE RUKSTINAT.

CHANGES IN THE CARTILAGE OF AN ANKYLOSED KNEE JOINT. A. L. ROSI, *Virchows Arch. f. path. Anat.* **284**:256, 1932.

The structure of a joint is the result of static and mechanical factors, and the relations of bone, cartilage and connective tissue are such as best adapt the joint to the dynamics of its function. Ankylosis sets aside the normal functions of a joint, while weight-bearing and locomotion subject the ankylosed joint to mechanical factors different from those that are operative in the normal joint. Roux made a gross study of the changes in the bones of an ankylosed knee joint. Rosi presents a histologic study of tissues of an ankylosed knee-joint. The ankylosis had occurred in early childhood, when developmental changes were still in progress in the structures of the knee. Tuberculosis of the joint at the age of 2 years had been followed by healing with preservation of some of the cartilaginous structures and by bony ankylosis of the joint in the flexed position. The child died at the age of 13½ years. During the period of inactivity, partial resorption of the persisting cartilage had occurred. When the joint was again subjected to mechanical stress and strain, proliferation of cartilage filled the defects with new-formed cartilage. The older cartilage underwent asbestos-like degeneration of its matrix, and where subjected to greatest stress, the cartilage had been replaced by fibrous tissue. Microfractures of bone and calcified cartilage occurred at points of greatest stress. The fatty marrow of the enlarged spaces of the original bone was supported by fine trabeculae of new-formed bone. Fixation of the joint in flexion had led to shifting of the insertion of the patellar ligament into the patella.

O. T. SCHULTZ.

HISTOGENESIS OF MESOGLIA. W. K. BELEZKY, *Virchows Arch. f. path. Anat.* **284**:295, 1932.

The origin and histogenesis of the mesodermal glial constituents of the central nervous system were studied in the chick and rabbit embryo and in new-born kittens. In the chick, on the fourth day of embryonic development, histiocytes can be recognized in the mesenchyme about the central nervous system. The histiocytes penetrate the nervous system with the choroidal and pial vessels. Within the nervous system, during further development, they become transformed into various types of cells, the character of which depends on their location and function. In the subependymal tissue and in the deeper white matter, they become drainage cells, which have no processes and bear a relation to tissue spaces and lymphatics. In the deeper layer of the cortex, they are transformed into oligodendroglia, and in the middle and superficial layers of the cortex, into Hortega cells, the function of which is the adsorption of materials from the cerebrospinal fluid. In the cortex, the processes of the cells are in contact with each other, but do not form a syncytium. The various cells of the mesoglia constitute a system of reticulo-endothelial origin. They retain the functional potencies of the reticulo-endothelial system and may manifest these functions in pathologic states. The glia of mesodermal origin, consisting of drainage cells, oligodendroglia and Hortega cells, may be termed the microglia, in contradistinction to the glia of ectodermal origin, or macroglia, composed of astrocytes.

O. T. SCHULTZ.

HISTOLOGY OF BALANTIDIUM COLITIS. H. HARMS, *Virchows Arch. f. path. Anat.* **284**:422, 1932.

In the case of *Balantidium colitis* that Harms had the opportunity to examine post mortem, there were multiple small ulcers in the colon. Some of the ulcers

were fresh, others were clean ulcers, and still others were in process of healing. In the earliest ulcers, it could be seen that the protozoa entered the crypts of the mucosa and penetrated between the epithelial cells. In the tissue of the mucosa they caused an inflammatory reaction that led to necrosis and to destruction of the overlying mucosa. The organisms did not penetrate the intact muscularis mucosae. Involvement of the submucosa developed when penetration occurred at the solitary follicles or by way of the capillaries or through areas of necrosis. The organisms apparently entered the capillaries readily, but were killed in the blood stream.

O. T. SCHULTZ.

BILATERAL GRANULOSA CELL TUMOR OF THE OVARIES WITH METASTASIS TO BONE. C. H. SOLTSMANN, *Virchows Arch. f. path. Anat.* **284**:466, 1932.

Tumors of the ovary derived from the granulosa cells of the follicles are not uncommon, but metastasis of such tumors has been infrequently reported. The tumor described by Soltmann was bilateral and occurred in a woman aged 43. Death on the tenth day after operation was due to paralytic ileus. The primary tumors were diffusely cellular. They contained folliculoid areas and columnar cell adenomatous fields. At necropsy, metastases were found in the sacrum. The folliculoid character of the tumor was much more evident in the metastases than in the primary tumor.

O. T. SCHULTZ.

GIANT CELLS IN AN APPENDIX REMOVED DURING THE INCUBATION PERIOD OF MEASLES. W. FINKELDEY, *Virchows Arch. f. path. Anat.* **284**:518, 1932.

In a previous article (**281**:323, 1931), abstracted in the ARCHIVES, the author reported the presence of giant cells of peculiar type in tonsils that had been removed during the period of incubation of measles. In the present article, he describes similar giant cells in an acutely inflamed, ulcerated appendix removed two days before the eruption of measles appeared, in a boy, aged 8. Finkeldey considers the giant cells of the lymphoid tissue of the tonsils and appendix a specific allergic reaction to the toxin of measles.

O. T. SCHULTZ.

THROMBO-ANGIITIS OBLITERANS. E. JÄGER, *Virchows Arch. f. path. Anat.* **284**: 526 and 584, 1932.

In two consecutive communications, ninety-four pages, Jäger gives an excellent and richly illustrated study of thrombo-angiitis obliterans, which since the time of Billroth and von Winiwarter has usually been referred to in the German literature as juvenile spontaneous gangrene. The study is based on four cases completely examined at necropsy and amputation material from twelve additional cases. A fifth case, in which necropsy was done, was included at the time of correction of proof, but does not receive so full a discussion. He also tabulates seven previously recorded cases that were examined post mortem. The earliest and what Jäger considers the most essential lesion of the disease is localized fibrinoid degeneration of the superficial part of the intima of the larger arteries. This leads to localized reactive cellular proliferation of the intima, which may be almost polypoid, and which leads to narrowing of the lumen. Such lesions are multiple and are found not only in the femoral artery and its branches, but also in the aorta, the coronary arteries, the circle of Willis and the arteries of the internal organs. The differences between the intimal lesions of thrombo-angiitis obliterans and those of arteriosclerosis are fully described and discussed, as are those of the early fibrinoid degenerative stage of acute rheumatic infection. The intimal involvement leads to red thrombosis. The latter process does not begin in the terminal vessels and propagate itself centrifugally, but occurs at the sites of intimal involvement of the larger arteries. The canalized tissue, which fills the larger arteries and which is a striking histologic feature of the later stages of the disease, is the result of organization of thrombi and not of inflammation

in the narrower sense. The intima peripheral to the areas of occlusion proliferates diffusely. This is a compensatory process, and is likewise noninflammatory. An active proliferative inflammatory reaction occurs in the terminal arteries and veins; the differentiation of this lesion from periarteritis nodosa is discussed. Occlusion of the larger veins is due to stasis thrombosis; this is followed by organization with canalization. Canalization of the venous thrombi may be adequate for return circulation; in the arteries it does not help to reestablish circulation. Healing of the intimal lesions of the larger arteries may occur, with the formation of areas of arteriosclerotic atheroma. In the early proliferative stage of the intimal lesions, giant cells, sometimes of Langhans' type, may be formed. Gangrene of the lower extremities need not be a feature of the disease. It is a late manifestation of a process that involves the arterial system widely. The disease, in Jäger's opinion, is a characteristic or specific vascular reaction, possibly on a constitutional basis, to a variety of causative agents. For this disease, he accepts thrombo-angiitis obliterans as the best designation. In the discussion and in the four closely printed pages of references due attention is given to the important American literature on the subject. O. T. SCHULTZ.

TONSILLAR CHANGES IN RHEUMATIC FEVER. F. KLINGE, *Virchows Arch. f. path. Anat.* **286**:333, 1932.

The tissue reactions that Klinge has described as characteristic of rheumatic infection occur in collagenous connective tissue. Such changes are therefore not to be expected in the reticulo-endothelioid lymphoid tissue of the tonsil itself. But in necropsy material rheumatic lesions have been observed in the peritonsillar tissues. Examination of tonsils removed during the acute or subacute stage of rheumatic fever has yielded inconstant results. In two pairs of such tonsils examined by Klinge there were numerous rheumatic lesions of the peritonsillar tissue, and in a third pair there were a few lesions, but in other tonsils the findings were negative. The results of examination of tonsils removed during a first or recurrent attack of rheumatic fever, taken in connection with the results of Sarafoff's examination of tonsils and tissues of the neck at necropsy, warrant the assumption that the rheumatic virus may enter the body through any part of the upper respiratory tract as well as through the tonsils. O. T. SCHULTZ.

PATHOLOGIC ANATOMY OF BRONCHIAL ASTHMA. W. PAGEL, *Virchows Arch. f. path. Anat.* **286**:580, 1932.

A man, aged 30, who had been subject to bronchial asthma for years, died suddenly in a paroxysm, evidently as the result of bronchial spasm. The changes that were noted in the bronchi and that Pagel considers characteristic of asthma were the presence of mucous spirals with crystals and eosinophils in the bronchial lumen, eosinophilous infiltration of the epithelium, plateau-like elevations and hernia-like depressions of the epithelium, thickening of the basement membrane, atrophy of the muscularis mucosae and hypertrophy of the smooth muscle of the submucosa. The mucus within the lumen of the bronchus comes in part from the mucous glands of the wall and in part from mucus degeneration of the epithelium. The plateau-like elevation of the epithelium is due to localized thickening of the elastic fibrils of the internal limiting membrane, and this in turn is compensatory to atrophy of the muscle fibers of the muscularis mucosae.

O. T. SCHULTZ.

MILIARY TUBERCLES IN THE SKIN IN MILIARY TUBERCULOSIS. P. GEIPEL, *Virchows Arch. f. path. Anat.* **286**:591, 1932.

To three previously recorded cases of generalized miliary tuberculosis in which he found tubercles in the skin, the author adds two similar cases. The tubercles

were situated either deeply or superficially in the corium; when they are superficial the epidermis may also be involved. All the cases were in nurslings. Geipel has never seen tubercles in the skin in miliary tuberculosis in adults. The subcutaneous tissue, on the other hand, practically uniformly reveals the presence of tubercles in miliary tuberculosis at all age periods.

O. T. SCHULTZ.

EFFECT OF TUBERCULOTOXIN ON THE LIVER. H. GUILLERY, *Virchows Arch. f. path. Anat.* **286**:605, 1932.

Previous work of the author, in which he ascribed the formation of tuberculoid granulomatous lesions and small areas of necrosis in the liver to the distant action of toxins derived from collodion sacs containing viable tubercle bacilli that had been implanted in the peritoneal cavity of rabbits, has been criticized. Some of his critics have obtained negative results by a similar method of procedure, and still others have ascribed the lesions to the action of bacilli rather than of their toxins. In the present series of experiments, Guillery used the phosphatide isolated from human tubercle bacilli by R. J. Anderson of the Rockefeller Institute. Eighty milligrams of the material in 10 cc. of distilled water was injected daily into rabbits intravenously. Each animal received from twelve to twenty injections and was killed at the end of the series of injections. In the liver there were found cellular lesions similar to those previously described. Necrosis did not occur. There was noted also the formation of Langhans' giant cells surrounded by normal liver cells, with no cellular infiltration. The author considers that the giant cells are derived from reticulo-endothelial elements that react as the result of their detoxifying function.

O. T. SCHULTZ.

CHANGES IN THE HYPOPHYSIS ASSOCIATED WITH ALTERATIONS IN THE MIDBRAIN. E. J. KRAUS, *Virchows Arch. f. path. Anat.* **286**:656, 1932.

Increased intracranial pressure is frequently associated with enlargement of the hypophysis, the enlargement being due to an increase in the size of the anterior lobe. The hypertrophy of the anterior lobe is due to hypertrophy and hyperplasia of its constituent cells, especially the eosinophil cells. It is requisite for the hypertrophy that the increased intracranial pressure is of sufficient duration and that the connection of the hypophysis with the midbrain is not disturbed. If the increased pressure is due to a condition that has caused destruction of the base of the midbrain or to a lesion of the stalk that separates the hypophysis from the midbrain, the anterior lobe undergoes atrophy rather than hypertrophy. The eosinophil cells are decreased in size and number. Kraus briefly describes twelve examples of atrophy associated with lesions of the midbrain or stalk. In one of these, which was a case of congenital dwarfism, separation of the hypophysis from the midbrain and failure of complete union of the anterior and posterior lobes, with resulting atrophy of the anterior lobe, were believed to be the result of congenital maldevelopment. From the study of these cases and of a much larger group in which intracranial pressure was associated with hypertrophy of the anterior lobe, Kraus concludes that lesions of the midbrain or hypophyseal stalk interfere with the liberation of the anterior lobe hormone and lead to atrophy of the anterior lobe. The condition of the gonads in cerebropituitary disease depends on the functional activity of the anterior lobe of the hypophysis and on the degree to which involvement of the midbrain interferes with the liberation of the hormone. The hypertrichosis of cerebropituitary disease may be the result of changes in the anterior lobe of the hypophysis or of changes in the gonads or of both combined. The obesity of cerebropituitary disease results from destruction or involvement of centers in the midbrain. The diminished function of the anterior lobe of the hypophysis resulting from such lesions of the midbrain may later lead to a decrease in, or disappearance of, the obesity.

O. T. SCHULTZ.

RECURRENT VENOUS THROMBOSIS OF INTERNAL ORGANS IN A CASE OF SUBACUTE SEPSIS. J. CATSARAS and A. SYMEONIDIS, *Virchows Arch. f. path. Anat.* **286:733**, 1933.

In a man, aged 42, an attack of grippal bronchopneumonia of fifteen days' duration was followed by thrombosis of the right and left femoral veins. Then there occurred severe pain in the region of the left kidney. Still later a severe attack of abdominal pain led to laparotomy and resection of the infarcted omentum. The various attacks were ushered in by chills and fever, and were accompanied by leukocytosis. Death occurred four and a half months after the onset of the illness. Thrombi of variable age and in various stages of organization were found in the pulmonary, portal, splanchnic, renal and splenic veins. Postmortem cultures of the heart's blood remained sterile, but the condition is ascribed to pneumococcic sepsis.

O. T. SCHULTZ.

CHRONIC OCCLUSION OF THE PORTAL VEIN. H. FLEISCHHAUER, *Virchows Arch. f. path. Anat.* **286:747**, 1932.

The author briefly reviews the previously reported cases of chronic occlusion of the portal vein, a condition which he contrasts with the sudden thrombosis of the portal and mesenteric veins that leads quickly to death by intestinal infarction. He presents two cases of his own, each in a man aged 52. In each case death was due to hemorrhage from esophageal varices. In the first case occlusion of the portal vein by an organized thrombus was consecutive to phlebosclerosis and thrombosis of the mesenteric and splenic veins, a process which, in its turn, is ascribed to a previous attack of appendicitis. A collateral circulation had been formed by way of the coronary and pyloric veins of the stomach. In the second case the organized thrombus of the portal vein was associated with an angiomatic plexus of veins at the hilus of the liver. For the explanation of this case the author subscribes to the view of Pick, that occlusion or obliteration of the portal vein and the associated cavernous hemangioma of the hilus of the liver are the result of embryonic maldevelopment.

O. T. SCHULTZ.

VASCULARITY OF THE PERIOSTEUM. H. NAUMER, *Virchows Arch. f. path. Anat.* **286:766**, 1932.

The cambium layer of the normal periosteum is described as having few blood vessels. When acutely inflamed, it is highly vascularized. The author injected turpentine into or beneath the periosteum of the femur and humerus of guinea-pigs and studied the tissue histologically at intervals of from six hours to twelve days. The cambium layer contained many engorged capillaries that were continuous with those of the haversian canals. The high degree of vascularity, as early as six hours after injection of the irritant, is interpreted as proof of the presence of numerous collapsed capillaries in the normal periosteum.

O. T. SCHULTZ.

THE NATURE OF ARGENTAFFIN CELLS. H. HAMPERL, *Virchows Arch. f. path. Anat.* **286:811**, 1932.

This is a critical survey of the technical methods used for the silver impregnation of tissues and of the conclusions to be drawn from the results of the application of such procedures. The discussion is limited to the impregnation of cells, and leaves out of consideration the impregnation of fibers, fibrils and intercellular substances. The varieties of cells that may be impregnated with silver depend on the method used. It is therefore meaningless to refer to a cell type as "argentaffin" unless the method used in bringing about the silver reaction is specified. Any single method may yield variable results if slight variations in technic are introduced. It is unwarranted to group together as an "argentaffin system" the various types of cells that may give a positive silver reaction, or to

base an assumption of the affinity of two or more cell types on the outcome of the silver impregnation technic alone. The author closes his article with a quotation from Goethe to the effect that it is much more important, in attempting to obtain a true knowledge of things, to note in what respects they differ than in what respects they may be identical. One is inclined to agree that this philosophy of Goethe's is still a good safeguard against the drawing of hasty conclusions based wholly on the outcome of a technical procedure.

O. T. SCHULTZ.

OCCURRENCE OF FATTY SUBSTANCES IN THE SPUTUM AND IN THE LUNGS. U. QUENSEL, *Festschrift, Upsala läkaref. förh.*, 1932, vol. 38, article 15.

Quensel points out that until recent years the function of the lung was considered only as far as it is concerned with the gas exchange of the organism. However, recent researches have revealed that in the pulmonary tissues various other processes, such as storage, digestion, resorption, filtration and elimination, take place. This report, however, is concerned only with the rôle of the lung in fat metabolism. For the cytologic examination of the sputums Quensel found staining with his solutions of methylene blue (methylthionine chloride, U. S. P.) and sudan or cresyl violet helpful. This method of staining is also suitable for unfixed frozen sections of lung tissue. In order to be able to study the position of the various cell elements in the mucus of the sputum it is advisable to fix the sputum globules in Bouin's fluid, embed them in paraffin and then stain the sections in the usual manner. To determine the occurrence of fat substances in the lungs the examination of unfixed frozen sections is best, and this method can also be used for sputums. In the sputums of healthy persons large cells can be demonstrated regularly, which may be considered as eliminated alveolar epithelial cells. They occur in various forms, with or without inclosures, and are identical with the so-called alveolar phagocytes. Quite frequently they are more or less laden with fatty substances, which for the largest part prove to be anisotropic. In addition to this, free fat is found in every sputum, generally the so-called myelin forms. In normal lung tissues fat substances of the same appearance and of the same type as those in the sputums are found regularly. The fat substances in the sputum apparently originate in the pulmonary tissues, where they occur either free or in the alveolar phagocytes. The sputum of patients with pulmonary tuberculosis contains, as the sign of an inflammatory process, a larger or smaller number of polymorphonuclear leukocytes. In addition to these, large cells of the same type as the alveolar phagocytes or the alveolar epithelium in the normal sputum are demonstrable. Their number increases as the sputum takes on the appearance of the normal sputum. Here again the large cells are more or less laden with fat that for the most part is also anisotropic. In view of the regular occurrence of fat substances in the normal sputum and lung, it seems likely that the fat-containing cells which are found in pulmonary tuberculosis originate in the healthy portions of the lung, and thus are not indicative of a pathologic process. All these observations seem to indicate that normally the lungs participate in some manner in the fat metabolism of the organism, because on the one hand there is an accumulation of fats in the lungs and on the other hand an elimination.

Pathologic Chemistry and Physics

UNIVERSAL CALCINOSIS. B. J. HEIN, *Arch. Surg.* **26**:389, 1933.

A girl, aged 6½ years, had diffuse deposits of calcium salts in the fasciae (universal calcinosis). The deposits diminished and improvement occurred with heliotherapy. The calcium salts apparently were removed by giant cell reactions, preceded by a granular disintegration of the masses. The patient has been under observation for four years.

EDWIN F. HIRSCH.

ENHANCED LETHAL EFFECTS OF X-RAYS ON *BACILLUS COLI* IN THE PRESENCE OF INORGANIC SALTS. W. D. CLAUS, J. Exper. Med. **57**:335, 1933.

When *B. coli* are irradiated by the x-rays in a series of salt solutions of tenth-molar concentration, the synergistic effect does not become appreciable until heavy salts are used.

FROM AUTHOR'S SUMMARY.

EXOGENOUS AND ENDOGENOUS IRON PIGMENT IN THE LUNGS. K. F. SCHEID, Beitr. z. path. Anat. u. z. allg. Path. **88**:224, 1932.

Lungs of iron miners were examined histochemically. The incineration method of Schultz-Brauns was helpful. In the pulmonary tissue the inhaled ferrous carbonate is changed into a pigment which, by histochemical methods, cannot be differentiated from hemosiderin. The same pigment forms after the inhalation of dust containing metallic iron. This pigment may be adsorbed by the coal particles in anthracotic lungs, and can then be detected only by incineration of fresh frozen sections. Coal particles will adsorb not only exogenous iron pigment but also endogenous hemosiderin, as in chronic congestion of the lungs.

C. ALEXANDER HELLWIG.

RELATIONSHIP BETWEEN TEMPERATURE AND OPTICAL PROPERTIES OF THE DOUBLY REFRACTIVE LIPOIDS IN THE ORGANISM. ZUISHUN IDA, Beitr. z. path. Anat. u. z. allg. Path. **88**:443, 1932.

Anisotropic fats were obtained from different organs of human cadavers, mammals, birds, amphibia, reptiles, fishes, insects and human parasites. It was determined at what temperature these substances lose their anisotropic properties or, on the other hand, regain them. Marked differences in this critical temperature were noticed in different species, in the different organs and in age. For instance, the lipoids of the testes and the suprarenals were anisotropic only at freezing temperature. The fatty substances of the intestines, cartilage, lymph nodes and brain showed anisotropism even at 100 C. (212 F.). In other organs the lipoids lost their anisotropic properties between room temperature and 100 C. These differences in optical properties between fats of different origin suggest that chemically the lipoids are not uniform substances.

C. ALEXANDER HELLWIG.

URIC ACID INFARCTS IN THE KIDNEY OF THE NEW-BORN. HANS HEINRICHS, Beitr. z. path. Anat. u. z. allg. Path. **89**:229, 1932.

Of 175 kidneys studied, 112 of which were from infants up to 3 weeks old and 63 from infants older than 3 weeks, 20 per cent had uric acid infarcts. The causes of death found in the positive cases were not in accord with the theory of Lubarsch that inflammatory processes predispose to the plugging of the renal tubules with crystals of uric acid. The highest percentage of infarcts was noticed in patients with nutritional disturbances (50 per cent). The opinion of Fahr, M. B. Schmidt and Aschoff that increased excretion and infarcts of uric acid in the new-born are caused by metabolic changes pertaining to respiration, nutrition and the regulation of heat during the first weeks of extra-uterine life is accepted. The enormous destruction of leukocytes during the first days of life may also play an important rôle.

C. ALEXANDER HELLWIG.

RELATION OF BILIARY SEDIMENT TO BILIARY CALCULI. R. SCHRADER, Beitr. z. path. Anat. u. z. allg. Path. **90**:304, 1932.

This article of sixty-seven pages is based on the microscopic study of the sediment of human bile obtained by postmortem puncture of the gallbladder and of dog's bile following a variety of experimental procedures. Five types of sediment or microliths are described. In the dog, simple stasis of bile in the gallbladder, such as follows ligation of a duct, leads to a marked concentration of bile

but not to the formation of microliths. Intermittent stagnation of bile, with the access of fresh bile, leads to the formation of green, waxy spherules and irregular masses (M1). These are composed of mucus and protein infiltrated by bile pigment. They were found also in human bile when there had been intermittent stagnation, of which process they are characteristic. In the dog, conglomeration of such material led to the formation of irregular pigmented concretions of considerable size; this was the only kind of concretion that could be produced experimentally in the dog. Similar concretions in the human gallbladder may be harder if they contain calcium. Infection and inflammation have no part in the formation of type 1 microliths. Pigment stones of the heavy earths may form in the biliary ducts as the result of stasis and toxic cholangitis. Microliths of type 2 (M2) were seen frequently in human bile post mortem and less frequently in dog's bile. They are brown, doubly refractile, rod-shaped or in the form of coarse needles arranged radially, and consist of a calcium-protein-bilirubin complex. Microliths of the third type (M3) have the same composition and physical properties as M2, but are spherical. These two types of microliths occurred when there had been central venous engorgement of the liver, of which condition they are symptomatic. Microliths of the fourth type (M4) were the kind encountered most often in human bile. They consist of calcium and an amyloid-like material. They occur only in the form of true spheres, which are doubly refractile and may reveal a laminate or radiate arrangement. They are indicative of disturbed hepatic metabolism (parenchymatous hepatitis) and may be especially numerous in the various forms of cirrhosis. They may be white, green or yellow. The fifth type of microlith (M5) consists of greenish-brown, granular, irregularly rounded masses about the size of leukocytes. Their composition is unknown. They are found constantly in bile from the gallbladder in association with cholecystitis, hydrops or calculi. Except in the case of the greenish concretions that are formed by the agglomeration of type 1 microliths, these various kinds of sediment have nothing to do with the formation of stones and do not make up the centers of calculi, though they may be incorporated in stones. The center of pure cholesterol stones and of the common pigment-calcium-cholesterol calculi is formed by a protein meshwork which is the result of cholecystitis or cholangitis.

O. T. SCHULTZ.

INORGANIC ASH SKELETON OF THE THYROID. G. MONSCH, *Beitr. z. path. Anat. u. z. allg. Path.* 90:479, 1932.

The quantitative relationships and the morphology of the inorganic ash of the thyroid were studied in eighty thyroids by the incineration method of Schultz-Brauns. Within the follicles the ash of the colloid in the spodograms varied considerably in its morphology and often appeared as radiate or laminate masses. These variations are due to the pressure developed in the colloid during the incineration and are dependent on the original consistency of the colloid. They are influenced also by the time and the temperature of incineration. The variable ash content of contiguous colloid nodules, revealed by the ashed sections, was associated with the variable content of the nodules in the parenchyma. No correlation could be detected between the staining reactions of the colloid and its ash content, nor was there any correlation between age and ash content. The parenchyma of the thyroids contained more inorganic ash than did the colloid nodules.

O. T. SCHULTZ.

SPECTROPHOMETRIC ANALYSIS OF THE COLOR-PRODUCING SUBSTANCES OF THE SERUM. PIUS MÜLLER, *Klin. Wchnschr.* 11:189, 1932.

Spectrophometric methods indicate the presence of three definite groups of chromophoric substances in normal and pathologic serums, hemoglobin absorbing at 414 millimicrons, lipochromes at 490, 460 and 425 millimicrons and bilirubin absorbing in a broad band with a maximal intensity of 450 millimicrons.

The absorption band for hemoglobin was found in all normal serums, but serums from patients with anemia, nephritis, diabetes mellitus and similar diseases

associated with a decrease in the hemoglobin content of the blood were more or less free from this band. The absorption bands for the lipochromes appear in the same positions in normal and pathologic serums, even in extracts made from the serums with purified petroleum benzine and carbon disulphide. Porphyrin, with an absorption band showing a maximal intensity at 406 millimicrons, was found in the serum of a patient with Biermer's anemia. The band disappeared when renal therapy was instituted. Müller believes that the intense yellow color in serum is not associated with bilirubin but is dependent on the hemoglobin content of the serum.

D. O. ROSBASH.

MAGNESIUM CONTENT OF THE BLOOD. ERWIN BECKER, *Klin. Wchnschr.* **11**:202, 1932.

The magnesium content of normal serum ranges from 1.8 to 2.3 mg. per hundred cubic centimeters, with an average content of 2 mg. In nephritic disease without renal insufficiency the value is slightly increased, while in acute and moderate renal insufficiency the value increases to an average of 3.5 mg. The increase of the magnesium content in renal insufficiency does not parallel the degree of functional disturbance in all cases. Erythrocytes contain more magnesium than the serum, and the fluids contain more magnesium than calcium. Muscle contains large amounts of magnesium.

D. O. ROSBASH.

A DIGITONIN MICRODETERMINATION OF CHOLESTEROL. P. O. MUHBACH and C. KAUFFMANN, *Klin. Wchnschr.* **11**:284, 1932.

A nephelometric method which is considered to be as accurate as the gravimetric method is described for the determination of free and esterified cholesterol in 1 cm. of blood or serum. Serum, blood or tissue is extracted with Bloor's alcohol and ether mixture. The free and combined cholesterol are dissolved in acetone, and after a detailed process of purification the free cholesterol is dissolved in alcohol. The addition of digitonin and water produces a colloidal turbidity which is compared with a standard solution of pure cholesterol. A portion of the acetone solution is saponified with concentrated sodium hydroxide, and the esterified cholesterol represents the total cholesterol content of the free cholesterol. From 0.2 to 0.8 mg. of cholesterol can be determined. More concentrated solutions should be diluted.

D. O. ROSBASH.

NONPROTEIN CARBON OF THE BLOOD IN CIRCULATORY DISEASES. F. KISCH, *Klin. Wchnschr.* **11**:1500, 1932.

The nonprotein carbon of the blood is increased in cardiac diseases. The highest values were obtained in cardiac edema and passive hyperemia of the liver. In disorders with edema small amounts of carbon compounds are excreted in the urine, and in diseases without edema, large amounts. With improvement the residual carbon content of the blood decreases and the amount of carbon excreted in the urine increases. Relapse is indicated by an increase of the residual carbon content of the blood.

D. O. ROSBASH.

Microbiology and Parasitology

THE ACCUMULATION OF IRON IN TUBERCULOUS AREAS. VALY MENKIN, *Am. J. M. Sc.* **185**:40, 1933.

Repeated intravenous injections of ferric chloride are followed by an accumulation of iron in caseous areas of tubercles and by a definite increase in the time of survival of tuberculous rabbits. Studies of the changes in weight and comparison of the pathologic involvement in the lungs of the control and experimental animals

at various intervals indicate that the intravenous administration of ferric chloride protracts the course of the disease. Repeated intravenous injections of ferric chloride retard the development of tuberculous lesions. This is found by comparing the extent of the pulmonary lesions in control and experimental animals that have had the disease for the same length of time.

AUTHOR'S SUMMARY.

THE NATURE OF THE NEGRI BODY. W. P. COVELL and W. B. C. DANKS, *Am. J. Path.* 8:557, 1932.

The cytologic evidence presented, with that contributed by other authors, together with the experimental evidence, is not compatible with the protozoan or organismal theories concerning the nature of the Negri bodies. The contention that they arise from constituents of the nerve cell as a result of the action of the virus is in agreement with our observations, but we consider the evidence for the participation of the mitochondria, neurofibrils and nucleolus as inconclusive. Both the Negri bodies and the smaller atypical lyssa bodies are probably formed by alterations in the basophilic Nissl substance, the fundamental ground substance of the cell, and by addition of variable amounts of basophilic material of nuclear origin. There is no evidence that organisms on the borderline of microscopic visibility are cloaked with these cellular components in accordance with the chlamydozoal hypothesis.

AUTHORS' SUMMARY.

A HISTOLOGICAL STUDY BY MICROINCINERATION OF THE INCLUSION BODY OF FOWLPOX. W. B. C. DANKS, *Am. J. Path.* 8:711, 1932.

Following incineration at high temperature, the fowl pox inclusion body leaves a grayish-white residue consisting of minute particles of mineral ash. The location of this residue corresponds topographically to that part of the inclusion body which stains pink with erythrosin-azur. The minute particles of mineral ash correspond in relative size and location to the "Borrel bodies" and are the inorganic residue of these structures. There is evidence that the "Borrel bodies," having, as they do, a relatively large amount of inorganic material in them, might well serve as a locus for adsorption of virus.

AUTHOR'S SUMMARY.

THE PATHOGENICITY OF THE BACILLUS OF CALMETTE-GUÉRIN. W. H. FELDMAN, *Am. J. Path.* 8:755, 1932.

With a strain of BCG obtained from Calmette of the Pasteur Institute, a deliberate attempt was made to increase its pathogenicity by subculturing the organism on a glycerinated egg medium. Transfers were made every thirty days. From each succeeding subculture, four guinea-pigs were given injections—two intracerebrally, one subcutaneously and one intraperitoneally. The report deals with data obtained after the organism had been subcultured on glycerinated egg medium for fifteen generations. Of a total of fifty-eight guinea-pigs inoculated, lesions histologically indistinguishable from those of tuberculosis occurred in the tissues of eleven, and cultures of acid-fast bacilli were obtained from each. Although the majority of the lesions occurred in animals that had been given intracerebral injections, one animal that was given an intraperitoneal injection and another that was given a subcutaneous injection died with lesions of a tuberculous nature. So far, attempts have failed to promote a succession of tuberculous lesions by the reinoculation into guinea-pigs of infective material from lesions. The particular strain of BCG studied is not devoid of pathogenicity for guinea-pigs, and the assertion that the organism is innocuous cannot be accepted without reservations. Subculturing the organism on glycerinated egg medium at monthly intervals for a period of fifteen generations did not markedly enhance its virulence.

AUTHOR'S SUMMARY.

Immunology

SKIN REACTIONS TO HEATED POLIOMYELITIS VIRUS. A. B. SABIN, W. H. PARK and C. W. JUNGBLUT, *Arch. Int. Med.* **51**:878, 1933.

There is at the present time no definite evidence for the existence of cutaneous allergy to the heat-inactivated virus of poliomyelitis in human beings, although such a possibility is not conclusively eliminated. Hence there is no basis for a skin test which would differentiate between susceptibility and resistance to the disease. Whether or not unheated virus may act differently in this respect is not known and must await the results of further investigations, which are naturally fraught with certain difficulties and remote dangers. FROM AUTHORS' SUMMARY.

ANTIGENIC RELATIONSHIP OF PROTEUS X19 TO TYPHUS RICKETTSIAE. M. RUIZ CASTANEDA and S. ZIA, *J. Exper. Med.* **58**:55, 1933.

There is a common antigenic factor in rickettsiae and Proteus X19 which explains the Weil-Felix reaction. AUTHORS' SUMMARY.

THE IMMUNOLOGIC SPECIFICITY OF BRAIN TISSUE. J. H. LEWIS, *J. Immunol.* **24**:193, 1933.

Suspensions of foreign brain tissue are strongly antigenic when injected into rabbits. A suspension of rabbit brain is not antigenic for the rabbit. Alcoholic extracts of all brains, including those of rabbit brain, are antigenic for the rabbit when activated with a foreign protein. Brain antisera produced with a suspension of brain tissue and those produced with an activated alcoholic extract of brain are indistinguishable as to their content of antibodies that react with organs. Brain antisera do not react with suspensions or alcoholic extracts of the liver, kidney, heart, spleen and lungs of homologous or all heterologous species tested. Neither do they react with blood serum, but they react strongly with both the suspension and the alcoholic extract of the brains of a group of animals representing mammals, birds and cold-blooded types. The brains of all animals tested are indistinguishable by complement-fixation reactions with an anti-brain serum. Brain antisera react strongly with either the suspension or the alcoholic extract of the testes of homologous and of all heterologous species tested. There is no qualitative difference between the reaction of a suspension and an alcoholic extract of brain, or between a suspension and an alcoholic extract of testes with an anti-brain serum. The spinal cord and all anatomic parts of the brain react similarly with an anti-brain serum. Lecithin (Merck's egg) does not react with an anti-brain serum. Cholesterol (commercial) gives marked reactions.

AUTHOR'S SUMMARY.

CUTANEOUS EPITHELIUM IN IMMUNITY RESPONSE. L. DIENES, *J. Immunol.* **24**:253, 1933.

In allergic (contact) dermatitis and certain cases of idiosyncrasy to drugs, the epithelium of the skin is probably sensitized. The hypersensitiveness of the epithelium develops by contact with the injurious agent in the same manner as the usual forms of hypersensitiveness. The tuberculin type of cutaneous reactions has many characteristics that suggest the direct participation of the cutaneous epithelium. The characteristic necrosis is often limited to the epithelium and a thin layer of connective tissue below it. The epithelium is involved early, before the macroscopic reaction is strong, and is often infiltrated with polymorphonuclear leukocytes, even in slight tuberculin reactions. The occurrence of necrosis has no direct connection with the size of the reaction or with the general sensitiveness.

AUTHOR'S SUMMARY.

COMPARATIVE PHAGOCYTTIC ACTIVITY OF MACROPHAGES AND POLYMORPHONUCLEAR LEUKOCYTES. BALDUIN LUCKÉ ET AL., *J. Immunol.* **24**:455, 1933.

When macrophages and polymorphonuclear leukocytes are afforded an equal opportunity *in vitro* for contact with various kinds of particulate objects, they show, in the absence of serum, a similar degree of phagocytosis toward most kinds of particles tested. A notable exception is observed with small particles of collodion, which are more readily ingested by macrophages than by polymorphonuclears. The presence of or sensitization with immune serum, or of its globulin fractions, promotes phagocytosis by both kinds of cells to an approximately corresponding degree. The mechanism of bacteriotropin action is the same for both kinds of cells; that is to say, the interaction of the antigen particle and the immune serum causes a specific combination with and deposition on the antigen surface of antibody globulin, as a result of which both kinds of phagocytic cells are enabled to spread on and engulf the sensitized particle.

AUTHORS' SUMMARY.

PHAGOCYTOSIS OF TYPHOID BACILLUS. STUART MUDD ET AL., *J. Immunol.* **24**:493, 1933.

Serums containing both flagellar and somatic antibodies against the typhoid bacillus and serums containing chiefly or only flagellar antibodies and chiefly or only somatic antibodies were prepared. These serums were tested in parallel agglutination and phagocytosis of flagellate typhoid bacilli to an equal degree by both macrophages and polymorphonuclear leukocytes. The bacteriotropin effect closely paralleled the agglutination. Sensitization to flagellar antibodies under the conditions of our experiments promoted phagocytosis of flagellate bacilli by both macrophages and polymorphonuclear leukocytes. The phagocytosis-promoting effect was inferior both in completeness and in titer to the agglutination; this difference is readily explained, however, by the secondary physical factors involved. The intracellular digestion of typhoid bacilli occurs with great rapidity in both types of phagocytes. The phagocytic behavior of the two types of cells was in essential agreement under the various conditions used in these experiments.

AUTHORS' SUMMARY.

ELECTRIC CHARGE OF ANTIBODIES. L. OLITZKI, *J. Immunol.* **24**:505, 1933.

Cataphoretic experiments with protein-making and protein-free agglutinins indicate that the results heretofore reported have been influenced by the protein present, and that the charge measured was that of the protein with which the agglutinin was associated. On the basis of the results with protein-free solutions, it seems that agglutinins (H and O type) carry a negative charge over a range of from pH 10 to 3.4 and below that point are too sensitive to acid reactions to make measurement possible.

AUTHOR'S SUMMARY.

ANTIGENIC PROPERTIES OF RABIES VIRUS. L. C. HAVENS and C. R. MAYFIELD, *J. Infect. Dis.* **52**:364, 1933.

The results of agglutinin absorption with massive doses of antigen indicate that all strains of rabies virus contain the same antigenic constituents, but in varying quantities. Neutralization of heterologous strains of virus can be accomplished, provided sufficiently large amounts of serum are employed. The evidence obtained from a comparison of three strains of rabies virus before and after passage through the rabbit indicates that, associated with other changes which have been observed in fixed rabies virus, there is a pronounced rearrangement of antigenic structure. Whether these several differences, though occurring concomitantly, are independent or whether they are correlated it is impossible to state from the evidence.

AUTHORS' SUMMARY.

STREPTOCOCCAL ANTITOXIN AND ANTISTREPTOLYSIN. E. W. TODD, L. J. M. LAURENT and N. GRAY HILL, *J. Path. & Bact.* **36**:201, 1933.

The antihemolytic and the antitoxic titers of serums from horses undergoing immunization with scarlet fever toxin frequently run parallel during the early stages of immunization. After prolonged immunization exceptionally high antitoxic titers may be attained without a corresponding increase of antistreptolysin. Serums from horses immunized with active streptolysin may contain large amounts of antistreptolysin, yet their antitoxic titers may remain relatively low. Patients with scarlet fever who give positive reactions to the Dick test on admission to the hospital may later give negative reactions without showing any change in the antistreptolysin titers of their serums. Rheumatic children whose reaction to the Dick test is positive may have abnormally high antistreptolysin titers. Antistreptolysin and streptococcal antitoxin are, therefore, distinct and separate antibodies.

AUTHORS' SUMMARY.

INFLUENCE OF HEAT ON DIPHTHERIA AND TETANUS FORMOL TOXOIDS. A. J. VAN DEN HOVEN VAN GENDEREN, *J. Path. & Bact.* **36**:319, 1933.

A number of comparative immunization experiments were made on guinea-pigs with heated and unheated diphtheria and tetanus formaldehyde solution toxoids. They led to the unexpected result that heating of tetanus toxoids from 60 to 70 C. improved their antigenic property considerably; heating to 80 C. had a rather deteriorating effect. With diphtheria toxoids, heating to 70 C. and higher had a deteriorating influence on the immunizing properties; heating to 56 C., however, resulted in improvement in a number of cases, but not in all. An explanation of this phenomenon cannot yet be given. Heating of diphtheria toxoid to 70 C. brought about a marked retardation of the flocculation reaction. In one case the flocculation did not appear at all. Even heating to 60 C. had a marked inhibitory influence.

AUTHOR'S SUMMARY.

IMMUNIZATION AGAINST YELLOW FEVER. A. W. SELLARDS and J. LAIGRET, *Arch. Inst. Pasteur de Tunis* **21**:229, 1932.

The results permit us to conclude that yellow fever virus, when weakened by numerous passages in the brain of mice, immunizes man against yellow fever. In the five subjects on whom observations were made, consecutive reactions to inoculation with the mouse virus were nil or insignificant. In a new series of seven trials, which will be the subject of a subsequent paper, three types of reactions occurred: febrile, delayed and atypical, which indicated the persistence in the mouse virus of a certain degree of activity for man, even after numerous passages.

FROM AUTHORS' CONCLUSION.

CROSS-IMMUNITY IN DIFFERENT FORMS OF TYPHUS. CHARLES NICOLLE and J. LAIGRET, *Arch. Inst. Pasteur de Tunis* **21**:251, 1932.

Tests of cross-immunity indicated that the typhus viruses studied—a historic strain (Tunis) and two animal strains (Mexico, Toulon)—are related. This is of practical importance, since they immunize against each other, but it does not prove identity. The preventive value of these viruses is not the same. The animal strains were more active against the historic strain than was this virus itself. Also they were more active against this virus than against themselves. In general, although they were of widely separated origin, the animal strains were more similar to each other than to the human virus. The results were the same, whether tested in the early stages, when the virus was still in the nerve centers (the period of premunition), or at a later period. This conclusion is also valid when the test is made with the virus employed for the first infection or with one of the other viruses. The results of tests of cross-immunity of typhus viruses are at variance with those of other tests in which the same method is used to differentiate them from other

exanthematic viruses. These tests differentiate the typhus viruses from the virus of Rocky Mountain spotted fever, as will be shown in subsequent articles, and from that of "button fever," as has been already shown by Burnet, Durand and Oliver.

AUTHORS' CONCLUSIONS.

Tumors

METASTATIC CARCINOMA OF THE HEART. C. H. MEAD, *J. Thoracic Surg.* **2**:87, 1932.

In cases of metastatic carcinoma of the heart, the lungs are invariably involved by primary or secondary carcinoma, hence the high frequency of pulmonary metastases generally may be a factor in increasing cardiac implants. Figures show, however, that in primary carcinoma of the lung there is less than 0.26 per cent cardiac metastasis. Direct extension is considered less likely than hematogenous metastasis by way of the pulmonary artery, the left atrium, the left ventricle and the coronary arteries. The author gives a complete case report with roentgenograms of the chest and a diagram of the massive primary bronchiogenic carcinoma of the right lung. The tumor extended through the right pulmonary vein to the left atrium, practically filling it, and continued through the mitral valve to end in a friable mass in the left ventricle. Mead also describes an invasion of the wall of the right atrium by carcinoma tissue, but it is not clear whether this was a direct extension or was metastatic. Associated findings were bronchopneumonia of the left lung and malignant infarct of the spleen. The cardiac involvement was not suspected clinically, and, as the author points out, few cases are diagnosed ante mortem.

J. STEWART.

PROPAGATION OF FUJINAMI'S FOWL MYXOSARCOMA IN DUCKLINGS. W. E. GYE, *Brit. J. Exper. Path.* **13**:458, 1932.

Fujinami's myxosarcoma of fowl has been propagated through eighteen generations in ducklings. The infective agent retains its power to infect chickens. In half-grown or in older ducks tumors form in response to injections of cell emulsions or of cell-free extracts, but the tumors retrogress.

AUTHOR'S SUMMARY.

PROPAGATION OF THE FUJINAMI FOWL-MYXOSARCOMA IN ADULT DUCKS. W. J. PURDY, *Brit. J. Exper. Path.* **13**:467, 1932.

Fujinami and Hatano found that a certain myxosarcoma of the fowl is propagable in ducks. Gye was able to confirm the observation in ducks of the Khaki Campbell variety, but only by using very young ducklings. It is now found that by the use of doses of tissue much larger than those given by Gye it is possible to propagate the Fujinami myxosarcoma in adult ducks of the Khaki Campbell variety through an indefinite number of generations. The greater efficacy of a large dose of minced tumor is not due to any greater energy of growth conferred on the cells of the resulting tumor. It is due to the fact that the resulting tumor starts in a greater number of primary foci, and reaches a correspondingly greater size before regressive changes have time to appear.

AUTHOR'S SUMMARY.

PROPAGATION OF THE ROUS SARCOMA NO. 1 IN DUCKLINGS. W. J. PURDY, *Brit. J. Exper. Path.* **13**:473, 1932.

Rous sarcoma 1 has been propagated in ducklings for five tumor generations and presumably could be propagated in these birds indefinitely. Very young ducklings were used. They were of the Khaki Campbell variety. For the propagation of the tumor it was found necessary to use minced tumor tissue as the inoculum. The dose was 0.5 cc., given intramuscularly. Filtrates of duckling-grown Rous sarcomas do not produce tumors in ducklings—neither do filtrates of fowl-grown Rous sarcomas. Filtrates of duckling-grown Rous sarcomas do produce tumors

in fowls, and do so just as readily as filtrates of fowl-grown sarcomas. Thus Rous sarcoma 1 growing in ducklings is exactly like a mammalian tumor growing in a mammal: Within the species it is propagable by means of cell grafts, but not by means of filtrates. It is only because filtrates of duck-grown Rous sarcomas give rise to tumors in fowls, an alien species, that a filter-passing agent can be demonstrated. Minced tissue prepared from fowl-grown specimens of Begg's endothelioma gives rise to growing tumors in very young ducklings, but the tumors are never large and they soon disappear. Filtered extracts of the fowl-grown endotheliomas never produce tumors in ducklings.

AUTHOR'S SUMMARY.

EFFECT OF TUMOUR REGRESSION AND TISSUE ABSORPTION ON THE SERUM. A. M. BEGG and H. A. A. AITKEN, Brit. J. Exper. Path. **13**:479, 1932.

Extensive bleeding or intratumoral injections of sodium oleate sometimes lead to regression of the Rous tumor in fowls. The presence of the Rous sarcoma does not increase the antitryptic property of fowl serum. The serum of fowls immune to cell inoculations of Rous sarcoma has high lipolytic power, and this statement applies also to the serum of animals which have received intramuscular or subcutaneous injections of surviving foreign tumor tissue. The presence of Rous, Mill Hill, "63," "37S," tar tumors or injected foreign tissue alters the serum of the tumor-bearing animals so that the point of flocculation with vanadate-acetic acid is displaced in the direction of lower pH .

AUTHORS' SUMMARY.

A FUNCTIONING ISLET TUMOR OF THE PANCREAS. W. G. BARNARD, J. Path. & Bact. **35**:929, 1932.

A woman, 40 years old, died from hypoglycemia and associated symptoms. At postmortem examination, a rounded tumor, 1.2 cm. in diameter, was found embedded in the head of the pancreas, projecting from its lower posterior border. The tumor was firm and grayish white. Microscopically, the general structure in the most characteristic parts of the tumor was strikingly similar to that of the islets. There were no metastases.

FAMILIAL AND BILATERAL TUMOURS OF THE CAROTID BODY. W. H. CHASE, J. Path. & Bact. **36**:1, 1933.

Two cases of "benign" neoplasms of the carotid body occurring in sisters have been described. In one instance the tumors were bilateral, appearing within an interval of six months. In the other the tumors and their histogenesis indicate that they are appropriately termed paraganglioma caroticum. The histologic study includes an investigation of the chromaffin-epinephrine relations and the demonstration of medullated and nonmedullated nerves. Factors possibly concerned in the occurrence of bilateral hyperplasia and neoplasia of the carotid body are indicated.

AUTHOR'S SUMMARY.

SIGNIFICANCE OF NERVE FIBRES IN HUMAN MALIGNANT NEOPLASMS. G. M. RYRIE, J. Path. & Bact. **36**:13, 1933.

A series of eleven cases of carcinoma was investigated to determine the presence or otherwise of nervous elements. The material used was obtained at operation. The technical difficulty of demonstrating with certainty axis cylinders was considerable. After extensive trial it was found that Gross-Bielschowski's silver impregnation method was the most satisfactory. When a portion of a nerve is destroyed by the advancing neoplasm, numerous new fibrils grow from the living axis cylinders of the proximal stump of the nerve trunk. These new axis cylinders not only grow within the perineural tube of the proximal portion, but penetrate into the neoplastic tissue. The process is exactly similar to what occurs after section of a peripheral nerve, and there seems no reason to suppose that the new-formed axis cylinders exert any "trophic" influence on the neoplastic cells.

AUTHOR'S SUMMARY.

RETICULO-ENDOTHELIOMATOSIS, OVARIAN ENDOTHELIOMA AND MONOCYTIC (HISTIOCYTIC) LEUKAEMIA. R. GITTINS and J. C. HAWKSLEY, J. Path. & Bact. **36**:115, 1933.

A case of bilateral ovarian endothelioma in an infant aged 1 year is described. The growth resembled a reticulo-endotheliomatous process and was somewhat different from any ovarian endothelioma heretofore recorded. The neoplasms, though extirpated, were followed by general reticulo-endotheliosis with the blood picture of histiocytic leukemia and a high lymphocytosis of normal type. Endothelioma of the ovary is rare. Several varieties are recognized. Including the one here reported, only twenty histologically authenticated cases of monocytic (histiocytic) leukemia are on record. The observation of focal neoplasia (ovarian endotheliomas) and general (histiocytic) leukemia in the same patient within a few weeks is put forward as evidence of the essentially neoplastic nature of this type of leukemia.

AUTHORS' SUMMARY.

MESOBLASTIC TUMORS FOLLOWING INTRAPERITONEAL INJECTIONS OF 1:2:5:6-DIBENZANTHRACENE IN A FATTY MEDIUM. H. BURROWS, Proc. Roy. Soc., London, s. B, **111**:238, 1932.

Tumors were produced in rats by the injection of 1-2-5-6-dibenzanthracene into the right hypogastrium. The compound was given as an emulsion of an olive oil solution of the substance in water, the final concentration of the hydrocarbon being 0.1 per cent. Definite tumors were obtained in eight of ten rats within from twenty-three to forty-eight weeks. One rat probably had a precancerous condition when killed at twenty-six weeks, and the remaining one was not examined. The distribution of the tumors is given. The general type of cell was the spindle cell, but giant cells were frequently seen, with occasional pronounced polymorphism. These types were found coexisting in the same animal. No metastases were observed in extraperitoneal regions. The respective parts played by the hydrocarbon and the fat in the carcinogenesis are undetermined.

L. E. SHINN.

PRODUCTION OF CANCER BY PURE HYDROCARBONS. J. W. COOK, I. HIEGER, E. L. KENNAWAY and W. V. MAYNEORD, Proc. Roy. Soc., London, s. B, **111**:455, 1932.

Tests for cancer-producing activity were made with several polycyclic, aromatic hydrocarbons. The only pure hydrocarbons which were found to produce carcinoma were 1-2-5-6-dibenzanthracene and some closely related compounds. The 1-2-5-6-dibenzanthracene shows undiminished carcinogenic power when highly purified. It has produced carcinoma when applied in a concentration of 0.003 per cent. Two hundred and thirty-three mice treated with this compound in benzene yielded seventy-seven epitheliomas and twenty-one papillomas.

L. E. SHINN.

PRODUCTION OF CANCER BY PURE HYDROCARBONS. J. W. COOK, Proc. Roy. Soc., London, s. B, **111**:485, 1932.

Evidence is presented for the carcinogenic power of 6-isopropyl-1-2-benzanthracene. Several compounds containing the 1-2-5-6-dibenzanthracene system were found to produce tumors. The 5-6-cyclopenteno-1-2-benzanthracene was found to be highly carcinogenic. Rings attached to the 1-2 and 5-6 positions of the anthracene ring system may produce particularly effective compounds.

L. E. SHINN.

INFLUENCE OF VITAL DYESTUFFS AND OF METALLIC COLLOIDS ON RESISTANCE TO TRANSPLANTABLE NEW GROWTHS. R. J. LUDFORD, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 1.

Experiments have been described which show that resistance to the growth of transplantable tumors can be lowered by vital staining (*Speicherung*). The

types of resistance to which this applies are natural resistance, etc. Evidence is adduced for believing that the lowering of resistance is the result of interference with the function of cells derived from lymphocytes and monocytes, which segregate acid dyes. Such cells appear in large numbers around the site of inoculation during the development of immunity, and also around the margins of reabsorbing tumors, tumors that induce concomitant immunity and irradiated tumors. When any such tumors are grown *in vitro* there is an extensive outwandering of mononuclear cells. The results of these experiments indicate the possible danger of overdosage in the treatment of cancer with colloids and semicolloids, in cases in which the body may be offering some resistance to the malignant growth.

AUTHOR'S SUMMARY.

EFFECT OF VITAL STAINING ON THE DISTRIBUTION OF THE BROWN-PEARCE RABBIT TUMOUR. L. FOULDS, Tenth Scientific Report of The Imperial Cancer Research Fund; 1932, p. 21.

Intravenous inoculation of the Brown-Pearce rabbit tumor closely reproduces the main features of metastasis from tumors implanted in the leg or the testis. Whatever the method of inoculation, tumors are rarely found in the spleen, and they are relatively uncommon in the lungs and the liver. Vital staining with trypan blue greatly increases the incidence of tumors in the spleen, lungs and liver after intravenous inoculation. The bearing of the experiments on some problems of metastasis in man is discussed. It is suggested that some organs, notably the spleen, resist the establishment of secondary deposits by a local mechanism similar to that which opposes the "take" of grafts in laboratory animals. This defense is probably dependent on the cells of the reticulo-endothelial system.

AUTHOR'S SUMMARY.

CHANGES IN CARBOHYDRATE METABOLISM INDUCED BY RADIUM IRRADIATION OF TISSUES. H. G. CRABTREE, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 33.

A study has been made of the effects of radium irradiation on the carbohydrate metabolism of surviving tumor and normal tissues. Also a limited number of observations have been made of metabolic changes induced by irradiating the Jensen rat sarcoma, rat testes and rat spleen *in vivo*. Studies *in vivo* are governed by the capacity of isolated tissues to survive in artificial mediums for relatively long periods. This is due to the latent period which must elapse before the criteria used in determining the effects produced by radiation become measurable. Tumors, testes and spleen were the only tissues of those examined which would satisfy this requirement. Irradiation *in vivo* with moderate doses gives results which are difficult to assess on account of the response of the whole animal. In the case of applications of large doses the accompanying impairment of function of vital organs introduces further complicating factors. The respiratory processes are always affected. *In vitro*, tissues under constant irradiation gradually lose their power of using oxygen after an initial period of some hours, during which no change is detectable. Control tissues meanwhile respire freely, though ultimately they suffer the same fate. Radium irradiation effects an acceleration of a naturally occurring degenerative process. Glycolytic processes are much more resistant to the damaging influence of radium irradiation. During the period of progressive decay of the respiratory power to a negligible value, glycolysis proceeds unimpaired. *In vivo*, similar effects are produced, though less rapidly. The delayed effect of radium irradiation on the Jensen rat sarcoma leads to a fall in magnitude of the respiration, or a damaging of its effectiveness in checking glycolysis, which results in the appearance of abnormally high aerobic glycolysis. On rat testis and spleen a fall in respiration is brought about without any corresponding rise of aerobic glycolysis. No differential action on the metabolism of tumor tissue, as against normal tissue, was observed as a result of radium irradiation. The conception that tumor tissue is inherently more vulnerable than normal tissue to irradiation is not supported.

AUTHOR'S SUMMARY.

EFFECTS OF RADIUM IRRADIATION ON THE SUCCINOXIDASE EXTRACTED FROM MUSCLE. H. G. CRABTREE, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 71.

The effects of radium irradiation on a typical oxydase have been studied. Using comparatively large doses of radiation, an irreversible inactivation has been demonstrated. The degree of inactivation is a function of the time of irradiation, the thickness of the layer of enzyme extract and the intensity of the energy emission. Beta-radiation and gamma-radiation produce the same effect, differing only quantitatively. The possible rôle of such inactivation in the irradiation of tumors is discussed.

AUTHOR'S SUMMARY.

EXPERIMENTAL OBSERVATIONS ON THE EFFECT OF RADIUM ON A PRECANCEROUS SKIN AREA. W. CRAMER, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 81.

The application of radium to a precancerous area of skin delays and even inhibits the development of malignancy. This effect was most marked when the precancerous conditions were not too far advanced and the dose of radium relatively large, as measured by the reaction of the skin. No evidence was obtained that radium, in the doses given, had an effect of breaking down the resistance of the skin to the development of malignancy. The application of radiotherapy in carefully graded doses to precancerous conditions in man is therefore strongly indicated as an effective measure for delaying and even preventing the development of malignancy. Further, when radiotherapy is applied to a fully developed malignant tumor in man, the possibility must be considered that a much larger part of the tissue or organ has been subjected to chronic irritation than that portion in which the malignant growth has developed, and that therefore even the apparently normal parts may be in a precancerous condition. For this reason the application of radiotherapy should extend over a much wider area than the malignant growth and its immediate neighborhood, in order to retard or prevent the subsequent development of a new malignant growth from the possibly precancerous cells. For instance, in the case of the breast, the treatment should extend over the whole organ.

AUTHOR'S SUMMARY.

EXPERIMENTAL OBSERVATIONS ON THE THERAPEUTIC ACTION OF RADIUM. W. CRAMER, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 95.

The conceptions concerning the therapeutic action of radium fall into two main groups: the view which attributes it to a local and direct action on the irradiated area, and the view which attributes the therapeutic effect to a generalized indirect action operating either by itself or in conjunction with the local action. Experimental analysis of the action of radium shows that a general indirect effect plays no part in the regression of a malignant new growth. In the conception of a direct local action one can distinguish between the view that radium has a selective destructive effect on the malignant cells and the view that the regression of a tumor is brought about by an action on the stroma, or bed, of a neoplasm. The question at issue is of fundamental importance for the rationale of radiotherapy. At present this is based on the assumption that every malignant cell has to be destroyed by a direct local action in order to bring about the regression of a malignant neoplasm. This conception would necessitate the application of radium continuously over a long period, or at frequently repeated intervals, in order to subject the malignant cells to the direct lethal action of radium when they are most sensitive to it—that is to say, when they are preparing for mitosis. No conclusive evidence, clinical or experimental, in support of this view has been offered. Experiments on tissue culture are not conclusive, because they do not represent the conditions of a malignant neoplasm growing in a living organism, since the effects on the tumor bed and the reaction of repair are left out of con-

sideration. The experimental analysis presented in this paper shows that irradiation of a neoplasm damages both the tumor cells and the tumor bed, and that regression of the tumor is brought about by a combination of these two effects and the process of repair following on the damage to the tumor cells and their bed. This is accomplished by a dosage and under conditions which preclude the possibility that every malignant cell has received directly a lethal dose. If this view, rather than that of a selective destructive action on malignant cells, is taken as a basis for radiotherapy, it follows that radium should be applied so as to produce a uniform effect on the tumor as a whole, surrounding it from all sides, and that the dosage should be such as to produce a maximal injury limited to the tumor as a whole and consistent with an active reaction of repair and with the integrity of the normal epithelial tissues, which play no part in this reaction of repair.

AUTHOR'S SUMMARY.

Medicolegal Pathology

PNEUMONIA IN KEROSENE POISONING. J. I. WARING, *Am. J. M. Sc.* **185**:325, 1933.

Nine cases of kerosene poisoning with pulmonary complications are reported. Leukocytosis, with an increased percentage of polymorphonuclears, was a characteristic symptom. The cholesterol content of the blood appeared to be reduced, but no other chemical change was noted. Experiments on animals tend to confirm the clinical opinion that serious and fatal cases of kerosene poisoning are due to the aspiration of kerosene into the lungs, with the production of inflammation, edema and potentially fatal pneumonitis.

AUTHOR'S SUMMARY.

SILICIC ACID CONTENT OF SILICOTIC LUNGS. C. HACKMANN, *Beitr. z. path. Anat. u. z. allg. Path.* **90**:623, 1933.

The silicic acid content of the lungs was determined quantitatively by a gravimetric method, which the author considers more accurate than some of the colorimetric methods recently described. The silicic acid content is expressed in percentage of dried, pulverized lung. The lungs of two new-born infants and of an 18 year old girl contained only traces of silicic acid. The normal lungs of three adults, aged 38, 59 and 73, respectively, had a silicic acid content of 0.238, 0.089 and 0.184 per cent, respectively. The main portion of the contribution deals with the gross anatomic, histopathologic and chemical findings in the silicotic lungs of thirty-seven stone workers of the Ruhr district. In this group of lungs the iron content was also determined. The quantity of the latter bore no direct relationship to that of silicic acid present. The latter substance was increased in every instance. If the lungs were divided into three groups, namely, those with slight or moderate silicosis, those with well marked silicosis and those with extreme silicosis, it was found that the quantity of silicic acid bore a close relationship to the degree of pathologic change. The lungs of the second and third groups contained 1 per cent or more of silicic acid. Sixteen of the lungs were tuberculous. Tubercle bacilli were present in nine of twelve lungs of the first group, those with a relatively low silicon content and slight silicosis, and in six of thirteen lungs of the third group, those with extreme silicosis and high silicic acid content. They were present in only one of twelve lungs of the second group, which showed well marked silicosis and a silicic acid content of from 2.5 to 3.5 per cent. In the case of two of the inhabitants of the Ruhr district, it was known that they had not been engaged in an occupation that subjected them to the inhalation of stone dust for fifteen and ten years, respectively, before death, although they had originally been stone workers. The lungs presented well marked silicosis and contained 3.05 and 2.49 per cent, respectively, of silicic acid. These findings are interpreted as indicating that silicon, when it has been deposited in the lungs, is not readily removed and continues its harmful action. Although the quantity of dust inhaled may be influenced by the type of breathing and by other mechanical factors, the degree of silicosis

appears to depend directly on the quantity of finely divided silicious material that reaches the air spaces of the lung. The pathologic and chemical findings in four cases of silicosis that came to necropsy at Göttingen are also presented. These persons had worked with various kinds of stone, but all unlike that of the Ruhr district. In this group, the silicic acid content of the lungs was increased, but the degree of silicosis could not be correlated with the quantity of silicon present, as in the Ruhr group. The findings in a group working with one kind of stone are not therefore exactly comparable with those of another group working with a different kind of stone. In three cases in which the amount of silicon in the liver and spleen was determined, the quantity was appreciably increased. In two of these cases, in which the kidney was also examined, this organ contained only traces of silicic acid.

O. T. SCHULTZ.

GROUP IDENTIFICATION OF STAINS OF HUMAN MATERIAL. L. CHRISTENSEN, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **20**:89, 1932.

Human semen, urine, saliva, amniotic fluid, tears, exudate and tissue contain the same receptors as the homologous blood corpuscles, by means of which the blood group of a person may be determined by appropriate tests. Only a small amount of material is required for such tests. In medicolegal work it may be of importance to identify the group of the blood or other material in stains of human origin.

HEMORRHAGES IN THE CERVICAL LYMPH NODES IN DEATH BY HANGING. L. JANKOVICH and J. INCZE, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **20**:122, 1932.

Above and below the mark made by the constricting cord one finds, in all the lymph glands of the neck, not only signs of congestion and stasis, but also hemorrhages, as a direct effect of the compressing force. These microscopic observations are never absent if the person was hanged while alive. Occasionally extravasations may be found in bodies which have been hanged after death, but such extravasations have no destructive character. Experiments made on animals disclosed that hemorrhagic infiltration of the cervical lymph nodes develops in a manner identical with that observed in human beings.

E. L. MILOSLAVICH.

EXPERIMENTAL DEATH BY DROWNING. M. HIRAI, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **20**:134, 1932.

From observations on submerged rats, the author divides the process of death into three phases: that of initial struggle followed by that of defenselessness and ending with the stage of apparent asphyctic death. At the beginning of the second stage the fluid enters the lungs and the respiratory function ceases. Even in the third stage attempts at resuscitation were successful, but only if the obstructing fluid was removed from the upper respiratory tract.

E. L. MILOSLAVICH.

PUPILLARY REACTIONS AFTER DEATH. K. RITTER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **20**:144, 1932.

Dilated pupils, as usually observed immediately after death, begin to contract equally not earlier than from seven to eight hours after death. This contraction is slow and gradual, until a width of from 2 to 3 mm. is reached during the next ten to fifteen hours. The pupils may then remain in this condition up to twenty hours after death. A slight dilatation and, later on, deformation follow. On the instillation of atropine, physostigmine (eserine), cocaine and epinephrine hydrochloride after death, the pupils exhibit the same reactions as they would have exhibited during life. With atropine, dilatation was obtained twenty hours after death, even after cadaveric rigidity of the muscles of the iris had set in.

E. L. MILOSLAVICH.

LETHAL POISONING WITH CHENOPODIUM OIL. A. IBRUS-MAEAER, Deutsche Ztschr. f. d. ges. gerichtl. Med. 20:158, 1932.

At the autopsy of a 3 year old boy whose death was attributed to poisoning with chenopodium oil, marked cerebral edema was striking, the brain weighing 1,500 Gm. Chenopodium oil, while abolishing the otolithic reflexes, stimulates the reactions of the semicircular canals, which explains the clinical aural symptoms, such as ringing in the ears, dizziness and partial deafness, the latter often persisting in nonfatal cases.

E. L. MILOSLAVICH.

ACTIVITY OF PERSONS WITH GUNSHOT WOUNDS OF THE HEAD. G. ROOKS, Deutsche Ztschr. f. d. ges. gerichtl. Med. 20:201, 1933.

In suicidal attempt, a man, aged 30, shot himself in the right temporal region; the outlet of the bullet was found in the center of the left side of the forehead. Two and a half days later, during which interval he was able to be up and around, the first symptoms of meningitis appeared, and death ensued three days afterward. Autopsy disclosed splintering of the frontal bones and destruction of the frontal lobes of the brain. In instances in which vital centers or motor areas in the brain have not been destroyed, the injured person is still capable of activity, provided that cerebral concussion does not render him unconscious.

E. L. MILOSLAVICH.

NATURE OF THE TRANSVERSE MARK IN THE NAILS IN ARSENICAL POLYNEURITIS. R. WIGAND, Deutsche Ztschr. f. d. ges. gerichtl. Med. 20:207, 1933.

In nonlethal cases of arsenic poisoning, about two months after the ingestion of the poison, all the finger-nails show a transverse, white-gray band, about 1 mm. in width (Mees mark), which finding is of great diagnostic value. The band is somewhat similar to that observed in thallium poisoning, and contains ten times as much arsenic as the apparently normal parts of the same nail. The Mees mark represents a deposit of arsenic owing to impregnation of the nail substance.

E. L. MILOSLAVICH.

THALLIUM POISONING. G. BERG and R. BERG, Deutsche Ztschr. f. d. ges. gerichtl. Med. 20:215, 1933.

Only three instances of murder by thallium poisoning are recorded in the literature. The clinical picture, as well as the observations at autopsy, are comparatively indefinite and negative. Swelling, congestion and hemorrhages of the mucous lining of the gastro-intestinal tract are usually present. Ordinary or routine chemical analysis of the organs fails to detect the presence of thallium. A special chemical examination is required. This is described in detail. The spectroscopic method, however, is a more sensitive, simpler and quicker means of detection.

E. L. MILOSLAVICH.

CHANGES IN THE SKIN CAUSED BY ELECTRIC CURRENT. G. STRASSMAN, Deutsche Ztschr. f. d. ges. gerichtl. Med. 20:239, 1933.

In lethal electrocution the gross and microscopic changes of the skin at the site of the electric lesion are identical with those which can be produced by electric current when applied to a dead body, when even deposits of copper may be found in the altered tissues. The intensity of the electric injury depends on whether the skin is moist or dry at the time of the contact; in the latter instance, the changes are more severe. The occurrence of a spark and steam, with the development of a crater-like defect, are regularly observed at the site of the positive pole, if the skin is dry. However, if the skin is moist, vesicles appear, which rapidly burst and then dry, and a yellowish, only slight depression of the skin is formed. At the site of the negative pole, sparks and the effects of burning never occur, and the micro-

scopic alterations are of lesser extent. A 40 year old person who came in contact with a 10,000 volt current sustained an extensive deep burn of the entire arm and died fourteen hours later. Autopsy disclosed diffused fat embolism of the lungs and moderate fat embolism of the kidneys and spleen, which finding must be considered in the cause of death.

E. L. MILOSLAVICH.

INFANTICIDE BY BURNING. WERNER RADTKE, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 20:267, 1933.

The ordinary tests for proof of live birth cannot be applied in cases of burning. Uninflated lungs with charred areas will float, and the stomach and intestines are rendered friable. If microscopic examination of burned parts of lungs discloses the presence of foreign material, this finding not only may be of importance in determining whether the infant was born alive, but may also lead to correct conclusions as to the cause and manner of death. The presence of soot in the respiratory tract must be carefully evaluated, since it does not conclusively prove that the infant was alive when burned. Sudan staining of the microscopic sections of the lung may be helpful in instances of aspiration of amniotic fluid. Since carbon monoxide cannot always be demonstrated in the blood taken from the cavities of the heart, microscopic analysis of the pulmonary tissue, even of the smallest charred remnants, should not be omitted, as it is the only remaining test which may yield important information.

E. L. MILOSLAVICH.

Technical

MICROTECHNICAL DEMONSTRATION OF INSOLUBLE LIME SALTS IN TISSUES. G. GÖMÖRI, *Am. J. Path.* 9:253, 1933.

Cut or saw thin blocks of fresh tissue from 1 to 2 mm. thick. Fix in an 80 to 96 per cent solution of alcohol, or boil in one of the solutions mentioned. After this, wash the blocks in distilled water for from three to four hours. Impregnate in a 1.5 per cent solution of silver nitrate for from six to ten days. Change the silver solution once or twice. Wash for from three to four days in distilled water changed daily four or five times, until the last washing water, when decanted, does not show the slightest turbidity when mixed with hydrochloric acid. Reduce in a 5 per cent solution of sodium hypophosphite. Before use add 4 or 5 drops of tenth-normal solution of sodium hydroxide to each 100 cc. of the reducer. Keep the blocks in the reducer for from four to eight days. Wash in running water for from three to four hours. Fix in a 3 to 5 per cent solution of sodium thiosulphate for two days; then wash in running water for at least twenty-four hours. Decalcify in a 6 to 8 per cent solution of sulphosalicylic acid. Wash, embed, and so on.

In sections prepared in this way lime salts stand out in deep black with striking clearness on an unstained background. The preparations are said to be durable.

PREGNANCY TEST: PREMATURE ESTABLISHMENT OF VAGINAL ORIFICE IN IMMATURE ALBINO RATS BY INTRAPERITONEAL INJECTIONS OF URINE. G. L. KELLY, *J. A. M. A.* 100:1010, 1933.

Intraperitoneal injections of from 5 to 15 cc. of urine from pregnant women will cause premature establishment of the vaginal orifice in the albino rat weighing from 30 to 40 Gm., usually within from seventy-two to eighty-four hours. Intraperitoneal injections of the same amount of urine from nonpregnant women will not cause such premature opening of the vagina. Two animals should be used, and the opening of the vaginas of both is read as positive; if the result is doubtful in one, the test should be repeated; if no result is obtained in either within ninety-six hours, the test is considered negative. If the vagina is open and the orifice obscure, one may see it by holding the animal by the neck and shoulder and pulling strongly on the base of the tail. In this maneuver the abdomen should not be compressed. The main advantages of the test are simplicity and ease of reading the result.

AUTHOR'S SUMMARY.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, March 23, 1933

PAUL KLEMPERER, *President, in the Chair*

THE THYMUS IN INFECTIOUS DISEASE. MELVIN C. KIMBALL.

It has been the impression in certain of the hospitals for patients with communicable diseases that there was an unduly high incidence of infections in persons who presented definite lymphoid hyperplasia at autopsy, which suggested the possibility of a constitutional factor as a contributory cause of death. This feeling was considerably strengthened during the epidemic of poliomyelitis in 1931, and it was resolved to test the truth of this impression by tabulating the weights of the thymus and spleen as representative organs. The weight of the spleen was much too erratic to serve as a reliable index. The weight of the thymus was adopted as more constant.

This report is based on the weights of 345 thymuses removed at autopsy in cases of infection. The weights are grouped according to the ages of the patients and tabulated against the duration of the illness in each instance, for each of the five major communicable diseases, poliomyelitis, diphtheria, scarlatina, measles and pertussis, as compared with the average figures for the entire series. Any such procedure is open to the criticism of the absence of agreement as to a table of normal weights. The average figures used for comparison in this study lie about midway between the low estimates of Bovaird and Nicoll and the high figures recorded by Boyd in her exhaustive studies.

In 80 cases of poliomyelitis, the average weight of the thymus paralleled and was constantly above the general average. In diphtheria, it again paralleled the general average, but dropped a little below it. In scarlet fever, the cases were too few in number to give a reliable index, and the weight seemed rather erratic, but tended to approach that in diphtheria. In measles, there seemed to be a low average figure in spite of the relatively short course of the disease. In pertussis, there was a definite diminution in the weight of the thymus, dependent in part on the nutritional stage of the child during the prolonged course of the disease. The particular point of interest in this study was the confirmation of the impression that the constitutional factor seemed to play a fairly definite part in poliomyelitis.

DISCUSSION

PAUL KLEMPERER: What is the histologic picture of the lymphatic tissue in poliomyelitis, not so much in the thymus, but in the spleen and lymph nodes? What is the condition of the so-called secondary follicles in this disease?

LAWRENCE W. SMITH: The follicles are almost regularly definitely enlarged, with large germinal centers, many of them showing beginning necrotic changes. This is true not only of the follicles in the spleen, but of the lymphoid follicles in the mesenteric and other lymph nodes and in Peyer's patches in the intestine.

PAUL KLEMPERER: Is the condition similar to diphtheria?

LAWRENCE W. SMITH: Yes, in the milder form.

AN UNUSUAL CASE OF FAULTY BLOOD GROUPING DUE TO AUTO-AGGLUTINATION. PERRY J. MANHEIMS and E. K. BRUNNER.

A patient was admitted to the hospital with a hemoglobin reading of 15 per cent, a red cell count of 780,000 and a blood picture of myelogenous leukemia.

A routine blood grouping seemed to show an A B (Jansky 4) group. Nevertheless, cross-matching with the blood of an A B donor showed agglutination of the donor's red cells by the patient's serum, and vice versa.

When the patient's blood was tested, marked auto-agglutination was present. A regrouping was done after washing the red cells with physiologic solution of sodium chloride, and this time there was no agglutination with standard serum of group 2 or 3. The blood was reclassified as of group O (Jansky 1), and cross-matching with the blood of an O donor, the patient's washed red cells being used, showed compatibility. A transfusion was given without reaction.

The assumption was that because of the extreme anemia of the patient the citrated suspension of red cells used in the original grouping contained a large amount of serum and the agglutination was due to the auto-agglutinins contained in this serum, or that the agglutination was due to the auto-agglutinins which the red cells of the patient had absorbed from her serum when kept at a temperature lower than that of the body.

DISCUSSION

MAX LEDERER: I think that this difficulty could have been avoided easily by taking a small amount of the patient's whole blood in citrate; if there is agglutination with both A and B serum, examination of the whole blood will reveal whether there is any auto-agglutination. Our laboratory makes it a rule whenever A B agglutination is observed to examine the patient's whole blood in citrate in order to avoid a mistaken conclusion that the blood is of group A B.

ARTHUR SCHIFRIN: In 1927, a specimen of blood from a patient whose condition was later diagnosed as hemolytic jaundice was submitted to the laboratory of Dr. Schwartzman at Mount Sinai Hospital. The blood was typed as of group 4. A donor of group 4 was called, and a cross-agglutination test was made, which showed the two specimens of blood to be incompatible. It was found that there was auto-agglutination. Since that time, in all cases of blood dyscrasia of any type, the custom has been to put a drop of saline solution on a slide whenever a determination has been made of group 4. Dr. Rosenthal pointed out at that time that in cases of blood dyscrasia this is necessary.

RALPH G. STILLMAN: These instances of auto-agglutination are much more frequent than one would expect from an inspection of the literature. One has constantly to bear in mind the possibility of auto-agglutination when making a test for transfusion, and when necessary one should check the results either by examining the patient's own blood in saline solution or by making a grouping by examination of the patient's serum with cells of known groups. My associates and I have found that the use of citrate is not altogether satisfactory, because it tends in many instances to slow up the reaction of the cells with the type serum used for grouping, and unless this is carefully watched, it is likely to introduce an error.

MENDEL JACOBI: Several instances of auto-agglutination have recently been encountered at the Beth Israel Hospital. One was in a case of acquired hemolytic jaundice, a second in a case of myelogenous leukemia, and a third in a fatal case of staphylococcic septicemia. In studying the question in some detail—and it is now made a routine practice at this hospital to look for auto-agglutination in all specimens of blood typed, at room, incubator and icebox temperature—a rather high incidence of this phenomenon was found distributed through all the blood groups. Recently I came across a family in which though none of the members showed any pathologic condition, auto-agglutination was prevalent, apparently distributed according to mendelian principles.

THE SO-CALLED BRENNER TUMOR OF THE OVARY (FIBRO-EPITHELIOMA MUCINOSUM BENIGNUM). ALFRED PLAUT.

In the last few years I have observed 8 cases of the so-called Brenner tumor (a detailed description is given in the *Archiv für Gynäkologie* **153**:97, 1933). The

growths were diagnosed as benign fibro-epithelial tumors with clear cells. All were small and firm. They were found accidentally, some of them at operation and 2 at autopsy. They did not give clinical symptoms. The uterine bleeding which was present in some patients could be explained by other causes.

One of the tumors, as shown in the slides, forms a small protrusion on the surface of a gyrate ovary. Under magnification with a hand lens a large calcific area can be seen and the largest of the epithelial masses are recognizable. A characteristic low power field shows the numerous, partly solid, partly hollow epithelial masses spreading as an irregular network through dense stroma which is similar to ovarian stroma. Some of the epithelial masses are surrounded by a thin (occasionally thick) hyaline coat. A few of the epithelial structures are entirely hollowed out. Generally, long sections show more solid portions, thus demonstrating that the hollowing-out is restricted to a part of the epithelial structure. At higher magnification the cells appear uniformly large and clear, with distinct outlines, similar to those in the upper layers of the epidermis. There are, however, no epithelial fibrils. The cells near the central cavity, which is filled with mucin, may be exactly like the other cells or they may arrange themselves like a lining epithelium. The formation of mucin sometimes takes place simultaneously at many spots. While in most of the epithelial structures the outer layers look like the others, there are some with a distinct basal layer characterized by smaller cells and deeper-staining nuclei. The formation of mucin and hollowing-out may result in destruction of the epithelium, leaving cavities seemingly in the stroma proper. In some specimens the hollowing-out leads to the formation of mucinous cysts, which are lined with a single layer of high cylindric, mucin-secreting cells such as are customarily seen in a pseudomucinous cystoma. Not only are there all gradations, from solid epithelial masses to glandular structures similar to and in some instances directly related to pseudomucinous cystoma, but on serial section the continuity between a characteristic Brenner tumor and ordinary pseudomucinous cystoma is evident. In the narrow glandular ducts in the wall of a pseudomucinous cystoma, the beginning hyalinization of the surrounding stroma indicates the spot where the neighboring sections will show continuity with a Brenner tumor.

The epithelium is the most important and active part of the tumor. One solid epithelial structure protruding from the main tumor into ordinary ovarian stroma is surrounded by stroma cells which are arranged parallel to each other and to the outline of the epithelial structure, forming a striking contrast to the irregularly interwoven ovarian stroma. There are other evidences that the tumor influences the surrounding tissue. The peritoneal epithelium has a tendency to grow around small tumors, and one of them seems completely isolated from the rest of the tissue by a peritoneal cleft.

A miniature Brenner tumor was found in the torn wall of a lutein cyst in the ovary of a young woman. As may be seen in the sections, only a short distance from this spot other very small characteristic Brenner tumors are located. In the same piece of tissue there are Walthard cell rests, solid as well as hollow. At points it is impossible to say whether the mass is a Walthard rest or a small portion of a Brenner tumor. In the same specimen continuity between epithelial masses of the Brenner tumor and the lining peritoneal epithelium can be observed in serial sections.

The Brenner tumor, like the ovarian fibroma, contains very few blood vessels. In the elastic tissue stain one sometimes sees a tumor between the remnants of elastic lamellae and blood vessels. This cannot be interpreted as a malignant growth. The blood vessels have been destroyed mechanically by pressure and kinking, and the tumor grows between the dead remnants of the vascular walls. The large amount of epithelial tissue in the Brenner tumor has led to its being considered malignant. None of the patients whom I have observed has shown evidence of recurrence or metastasis. The cases, however, are recent (none having been observed for more than four years). When a Brenner tumor is found together with metastatic carcinoma, the diagnosis may become difficult.

The name proposed, "fibro-epithelioma mucinosum benignum," is intended first to designate the unusual feature that mucin is formed within a nonglandular epithelial tissue. This, however, takes place in normal tissues as well, for instance in the prostate of the new-born and occasionally in the prostate of the adult. I consider the benignancy of the tumor to be sufficiently established to permit the inclusion of the term "benignum" in the name. I should like to include in the name a reference to the compact character of most of the tumors, but the presence of many cysts does not permit this.

The number of cases described is not large enough for statistical evaluation. In most features these cases resemble the cases reports of which were collected by Robert Meyer. It is not yet known how frequent, or how rare, the tumor is. Brenner, in 1907, observed 3 cases within one year in Frankfurt; Meyer saw only 4 in the course of twenty years. It is astonishing that I have seen 8 in New York within five years. Statistics on the frequency of the tumor should be based on autopsy material as well as on gynecological material. The fact that in my gynecological material the tumors were found combined with other ovarian tumors does not prove anything, since these operations were undertaken for the symptoms caused by the other tumors. I have had the ovaries in 75 cases carefully sectioned without finding a Brenner tumor. In cases in which a Brenner tumor has been present in one ovary, nothing definite has been learned about the condition of the other ovary. In 1 instance only (that of Schiffmann) was a Brenner tumor found in both ovaries, and it was of microscopic dimensions. A complete serial examination of the other ovary was made in 1 of my cases, but no Brenner tumor was found, nor even Walthard rests. The Brenner tumor can develop in ovaries containing many Walthard rests and in ovaries containing none. One may consider the development of a Brenner tumor from a Walthard rest as tumorous growth without differentiation, while certain pseudomucinous cystomas represent tumorous growth with specific differentiation. I do not believe that all the so-called Walthard rests have existed from the embryonic period; I am convinced that they can originate during life from the peritoneal epithelium. On this point I am in full accord with Robert Meyer.

The youngest patient in my series was 20 years old, and the oldest, 73. No Brenner tumors have been reported in children. But the Walthard rest which Akagi found in the ovary of a 9 year old girl may be called the epithelial part of a very small Brenner tumor.

DISCUSSION

PAUL KLEMPERER: It is obvious that there is no discussion from the floor because of the rarity of these tumors. At Mount Sinai Hospital only 2 tumors of this type have been seen in the last twenty years. I think that in Dr. Frank's book (*Gynecological and Obstetrical Pathology*, New York, D. Appleton and Company, 1922) there is a picture of a tumor called a folliculoma which belongs to this type, and this shows that the growth has not been recognized until lately. Dr. Plaut deserves the credit for having called attention to these tumors.

In regard to the formation of mucin in other locations, I should like to mention, since Dr. Plaut spoke of such instances in the prostate, Brunn's epithelial nests in the bladder. One finds them frequently, and it is interesting that from these cell nests with formation of mucin malignant tumors may originate. I recently saw one in a normally formed bladder; it is in the exstrophic bladder that one most often finds the mucous cell nests which lead to carcinoma.

ALFRED PLAUT: The case at Mount Sinai Hospital that Dr. Klemperer alluded to is that of Geist, I believe. He closed his paper in 1922 with the remark that he did not want to give the tumor a name; and he described it merely as originating from an embryonal rest. The further development has substantiated that.

As to cell nests in the bladder, true gelatinous carcinomas may arise from such nests even as high as in the renal pelvis. I saw a gelatinous carcinoma in the pelvis of a kidney which could not be explained in any other way.

I may repeat that I had had the ovaries in 75 cases sectioned in very thin slices in the hope of finding a Brenner tumor and have not found any.

MALIGNANT NEPHROSCLEROSIS AND PERIARTERITIS NODOSA. SADAŌ OTANI.

Two cases are presented of malignant nephrosclerosis associated with periarteritis nodosa in other organs. Within the kidneys but one vessel was found which showed the typical fibrinoid necrosis of the media. As vascular alterations these organs presented chiefly the excessive intimal proliferation of the interlobular arteries and the necrosis of the arteriolar walls that have been described in malignant nephrosclerosis. The association with periarteritis nodosa raised the question whether these observations did not conclusively prove the inflammatory nature of the vascular alterations in malignant nephrosclerosis, a contention championed by Fahr. However, the prolonged duration of the disease and the finding at autopsy of peracute periarteritic lesions associated with advanced sclerotic lesions of the renal vessels suggested that the association might just as well be a coincidence.

DISCUSSION

ALFRED PLAUT: Arteriolitis comes into its own rather slowly. When one pays special attention to the arterioles, one finds arteriolitis more frequently than one would expect from the current literature. Some of the members of the society may remember the paper presented about a year ago by Drs. Helpern and Trubek (Isolated Necrotizing Arteritis and Subacute Glomerulonephritis in a Case of Gonococcal Endocarditis, *ARCH. PATH.* 14:266, 1932). The gallbladder is a favorite site for periarteritis nodosa. Only a short time ago a patient was operated on in Beth Israel Hospital for acute cholecystitis, and the slides gave a picture of periarteritis nodosa. It is not yet known what other organs of this patient may contain the same lesion. Lesions which might be called periarteritis nodosa have been found in the testicles, the gallbladder and the eyes of patients with general infections—for instance, recently in a child with a general streptococcal infection probably starting from streptococcal pneumonia. How far these lesions conform with what is called periarteritis nodosa is another question. The present interest centers about the arteriolitic lesions found in people who do not suffer from infectious disease. I have seen arteriolitis in about 30 appendixes in the last few years. These were not inflamed appendixes, but those removed in the course of gynecological operations and other appendixes without inflammatory lesions. The common link seems to be an immunologic condition, some susceptibility of portions of arteries or arterioles which leads to necrosis. Whether or not the degenerative change in the wall of the vessel is followed by an inflammatory reaction depends on unknown conditions. I have expressed the feeling before that probably the pathology of the arterioles will occupy more space in textbooks of pathology a few years from now. Dr. Moon in Philadelphia told me that similar lesions occur in rabbits with experimental streptococcal infections. I accidentally saw an arteriolitic lesion in the skin of a mouse.

PURULENT THROMBOPHLEBITIS OF THE PULMONARY VEIN. WILLIAM ANTOPOL and COLEMAN B. RABIN.

Cases of infective thrombophlebitis of the pulmonary veins may be divided into two groups, the first consisting of those in which the small branches are involved, and the second in which there is infection of the larger radicles. Cases of the first type are often discovered only by the aid of the microscope. In these cases the thrombophlebitis may give rise to sporadic metastatic lesions in various parts of the body. In those of the second type a general infection ensues and gives rise to the picture of sepsis. Since the pulmonary veins enter the left side of the heart, emboli and infected infarcts are common.

The material on which this report is based consisted of 14 cases in which the larger pulmonary veins were involved. In 11 of these cases the initial focus

of infection was situated within the lung. The pulmonary disease was of a destructive type, either suppurative or gangrenous.

In 4 of the cases the primary lesion was suppurative bronchopneumonia. In 2 of these *Streptococcus haemolyticus* was the causative organism; in 1, *Pneumococcus* type III, and in 1, either an anhemolytic streptococcus or a pneumococcus of type IV. In 7 cases the primary lesion was a gangrenous abscess of the lung, and the invading organisms consisted of a mixture of anaerobic bacteria. In 2 of these cases the general invasion was probably the result of laceration or incision of a vein at operation. The healing of the lesions is demonstrated by the finding of a smooth-walled arteriovenous aneurysm two years after spontaneous healing of a gangrenous pulmonary abscess.

Thrombophlebitis of a pulmonary vein may occur in association with metastatic lesions of the lung secondary to a primary focus of infection somewhere else in the body, and it may serve to cause a general infection or sepsis even if the original infection is inadequate to do so. Three of our cases fall into this group. The importance of these lesions in maintaining a general infection again depends on the size of the vein invaded.

PYLEPHLEBITIS COMPLICATING GANGRENOUS PULMONARY ABSCESS. C. B. RABIN and SYLVAN MOOLTEN.

Suppurative pylephlebitis is usually secondary to a suppurative lesion within the gastro-intestinal tract. Its association with putrid pulmonary abscess is exceedingly rare according to the literature; nevertheless, we have observed 5 cases. The transport from the focus of suppuration within the lung is always through an infection of a pulmonary vein in the region of the abscess which enters the general circulation by way of the left side of the heart. Infection of small veins gives rise to single metastatic foci, and infection of larger veins, to multiple foci throughout the body.

The mechanism underlying suppurative pylephlebitis complicating pulmonary abscess is found to be a metastatic or an embolic abscess within the spleen. Infection of a branch of the splenic vein is demonstrable at the site of this abscess and produces involvement of the trunk of the splenic vein, with subsequent spread into the portal vein and its intrahepatic radicles. The pylephlebitic abscesses may secondarily involve the hepatic veins from which the bacteria enter the greater venous circulation. Metastatic pulmonary abscesses may occur in this manner.

Jaundice was present in 3 of our 5 cases of pylephlebitis complicating pulmonary abscess; it was not observed in any other case of pulmonary abscess in a series comprising well over 250 cases. It may be considered pathognomonic of this complication. Marked swelling and tenderness of the liver support the diagnosis. (Direct transdiaphragmatic spread of a pulmonary abscess into the liver has never been observed.)

Subphrenic abscess on the left side, associated with pulmonary abscess, is usually of metastatic origin. In 1 of our cases it followed perforation of an abscess of the spleen; in another, perforation of an abscess in the left lobe of the liver. We have never seen it result from transdiaphragmatic extension from the lung, although 2 cases of this type have been reported by others. When other metastatic foci are present—e. g., in the brain, skin, kidneys or extremities—together with the clinical evidences of pylephlebitis in a case of pulmonary abscess, one may assume the existence of gangrenous thrombophlebitis of one of the large branches of the pulmonary vein as the source.

DISCUSSION

SOLOMON WEINTRAUB: I have brought the specimens from the cases mentioned by Drs. Antopol and Rabin. In one of these cases the specimens show a pulmonary abscess with pulmonary thrombophlebitis and an abscess in the interventricular septum of the heart. This is the case of a colored man, 22 years of

age, who was admitted to Harlem Hospital complaining of abdominal pain, vomiting, tenderness in the abdomen and productive cough. The patient lived about five days, during which time the question arose whether the condition was a beginning lobar pneumonia, because of the productive cough and chills and fever. Roentgenograms were taken which showed the condition clearly. A flat plate was taken to rule out a ruptured gastric ulcer; the diaphragm was rather high on the left with a rather low splenic flexure, indicating that there was something present which pushed the left side of the diaphragm up and the splenic flexure down. The roentgenogram of the lung revealed a definite level of fluid. At autopsy the patient showed, in addition to the pulmonary abscess, pulmonary phlebitis, as shown in the specimen, 2 abscesses of the interventricular septum, infarcts of the liver and left kidney and ruptured infarcts of the spleen with a left subdiaphragmatic abscess. There was phlebitis of the splenic vein, which explained the abscesses in the liver.

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of infection was situated within the lung. The pulmonary disease was of a destructive type, either suppurative or gangrenous.

In 4 of the cases the primary lesion was suppurative bronchopneumonia. In 2 of these *Streptococcus haemolyticus* was the causative organism; in 1, *Pneumococcus* type III, and in 1, either an anhemolytic streptococcus or a pneumococcus of type IV. In 7 cases the primary lesion was a gangrenous abscess of the lung, and the invading organisms consisted of a mixture of anaerobic bacteria. In 2 of these cases the general invasion was probably the result of laceration or incision of a vein at operation. The healing of the lesions is demonstrated by the finding of a smooth-walled arteriovenous aneurysm two years after spontaneous healing of a gangrenous pulmonary abscess.

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C. B. RABIN: To me just those cases which Dr. Klemperer spoke about are the most interesting—those in which there is a history of sore throat and cough and the condition is considered grip clinically, but in which chills and embolic phenomena develop while the patient is under observation. In both of the cases reported there were the signs and clinical symptoms of sepsis, and a blood culture showed *Streptococcus haemolyticus*. The nature of the cases was obscure clinically, but it need not have been had the possibility of phlebitis of the pulmonary vein in association with the pulmonary lesion been given consideration. Small lesions occur in the lung in grip or influenza which may give no physical signs. However, roentgen examination in each of these cases showed a pneumonic process of moderate extent. This finding, together with the presence of *Streptococcus haemolyticus* in the blood culture, in the absence of any further obvious focus, could have led to the proper diagnosis.

I wish to say a word concerning operations on the lungs, especially in the suppurative diseases. Surgeons now have no hesitancy in cutting into the substance of the lung; they have no fear of hemorrhage, and they feel that cutting into a lung is just like cutting into any other tissue. In most respects, this point of view is correct, yet cutting into a pulmonary vein which leads to the left side of the heart incurs the danger of allowing bacteria as well as air to enter the circulation. The danger of washing bacteria from a pulmonary abscess or a bronchiectatic cavity into the circulation is practical as well as theoretical. It appears to me that to prevent this dangerous complication surgeons should use, instead of the scalpel, the cautery, which will seal off the pulmonary vessels and prevent the entrance into the pulmonary veins of infective material.

The concept of Nathan, who belongs to the Schottmüller school, is that the most important mechanism for the maintenance of a constant invasion of the blood stream, which is what is meant by sepsis, is involvement of the pulmonary veins as a secondary focus. He gives the impression that, given a focus somewhere in the body, there would be no sepsis if there were not at the same time secondary involvement of the pulmonary veins. I must take exception to this rather revolutionary view. I am sure that those who have observed cases clinically have seen any number in which there was a focus somewhere in the body that gave rise to a generalized sepsis and in which there was no demonstrable involvement of the lung either clinically or on roentgen examination. The metastatic abscesses are always visualized roentgenologically, if so examined. Yet there are many cases, especially in the early phases of infection, in which the pulmonary substance is not involved, and in which, therefore, there is no infection of the pulmonary veins. One must also bear in mind that although infection of the microscopic vessels of the lung may give rise to metastatic phenomena in various parts of the body, it is not to be considered a cause for sepsis. These small vessels are thrombosed very early. Occasionally bacteria or a clump of bacteria may pass through them into the greater circulation, but it is only when the large vessels are involved that sepsis or generalized infection really takes place.

Regular Meeting, April 27, 1933

PAUL KLEMPERER, *President, Presiding*

TRICUSPID STENOSIS ASSOCIATED WITH CHYLOUS ASCITES. DAVID PERLA.

A woman, aged 48, with a history of rheumatic polyarthritis five years prior to admission and repeated attacks of congestive failure during the past three and a half years, was admitted to the hospital complaining of dyspnea, orthopnea and swelling of the abdomen.

On examination the patient was found to be obese, cyanotic and dyspneic. There was marked engorgement of the veins of the neck. The heart was

moderately enlarged, with evidence of mitral and aortic valvular disease and auricular fibrillation. The liver was large, hard and nonpulsating; ascites was present. There was edema of the lower extremities. A large amount of milky fluid was aspirated from the abdominal cavity. The total fat content of this fluid was 0.24 per cent. The patient had to be tapped every three days. The cyanosis increased. A chill and high fever developed, followed by stupor and death, six months after admission.

At autopsy healed rheumatic lesions of the aortic and tricuspid valves with mitral stenosis and tricuspid stenosis were found. The right auricle was enormously distended. The pericardium was distended with clear serous fluid. There was evidence of chronic passive congestion of the viscera. The abdominal cavity contained 3 liters of milky fluid. It is suggested that the marked venous tension in the left subclavian vein due to the tricuspid stenosis prevented the flow of lymph from the thoracic duct into the vein with consequent obstruction and chylous ascites.

SUBACUTE BACTERIAL ENDOCARDITIS WITH RUPTURE OF THE SUPERIOR MESENTERIC ARTERY AND FATAL HEMORRHAGE. DAVID PERLA.

Since June, 1931, a man, aged 34, with no antecedent rheumatic history, had had repeated attacks of stinging pain in the finger tips, toes and palms, associated with tender red areas that subsided in from a few hours to a few days. In October, a left hemiplegia developed from which the patient gradually recovered. Since that time he had complained of fever, weakness and sweating. In August, 1932, enlargement of the spleen was first noted.

On examination he was found to have the signs and symptoms of subacute bacterial endocarditis with cardiac hypertrophy, mitral stenosis and insufficiency, aortic insufficiency and enlargement of the liver and spleen. There was secondary anemia. The urine contained albumin and red blood cells. The case ran a septic course for a period of three months. In April, 1933, the patient complained of mild diffuse abdominal cramps. There was no blood in the stools. On April 14 he suddenly went into collapse and died.

At autopsy the following lesions were found: subacute bacterial endocarditis of the aortic and mitral valves, aortic insufficiency, healed rheumatic endocarditis of the aortic valve, multiple healed infarcts of the spleen and kidneys and acute embolic glomerulonephritis. There was also a mycotic aneurysm of the superior mesenteric artery with rupture and hemorrhage into the peritoneum and mesentery. The peritoneal cavity contained 1,700 cc. of partly clotted blood. The mesentery was markedly thickened and dark purplish. There was an extensive hemorrhage dissecting the layers of the mesentery and producing marked edema of the ascending and transverse colon.

LYMPHOSARCOMA OF THE SECOND PORTION OF THE DUODENUM WITHOUT JAUNDICE. DAVID PERLA.

A man, aged 51, was admitted to the hospital complaining of loss of weight, vomiting after meals, weakness and abdominal pain of five months' duration.

Examination revealed a movable tender mass in the epigastrium, the size of an orange, and enlarged cervical, axillary and inguinal lymph nodes. There was secondary anemia. Two years previous to admission the patient noticed lumps in the left side of the neck, which decreased in size under roentgenotherapy, but later reappeared. The stools were positive for blood. Roentgen examination revealed an obstruction in the distal duodenum, causing delayed gastric emptying. The patient continued to vomit, became emaciated and died, three weeks after admission.

At autopsy a large lymphosarcoma was found in the second portion of the duodenum, encircling the wall, with ulceration within the lumen. It compressed the head of the pancreas without invasion and circled the papilla of Vater and the common bile duct, but did not produce obstruction. There was no jaundice.

Metastases were present in both kidneys, and in the cervical, axillary, inguinal and retroperitoneal lymph nodes.

CARCINOMATOUS THROMBO-ENDARTERITIS OF THE PULMONARY VESSELS. E. B. GREENSPAN.

While the etiology of certain types of obliterative endarteritis of the pulmonary vessels is not clear, there is one type in which the pathogenesis is known. In this group, the intimal proliferation is the direct result of neoplastic invasion of the lung, and the presence of the obliterating endarteritis causes a generalized narrowing of the pulmonary arterioles and the smaller arteries, right ventricular hypertrophy and finally right ventricular cardiac failure.

Four cases were studied, two of which clinically presented the features characteristic of failure of the right ventricle. In the third case, the symptoms were entirely gastro-intestinal, except for sudden cardiac collapse, in which the patient died. In the fourth case, the abdominal symptoms were associated with progressively increasing dyspnea.

At autopsy the first three cases mentioned revealed a scirrhus adenocarcinoma of the stomach. The primary tumor in the fourth case was an adenocarcinoma of the sigmoid colon. At necropsy in all four cases the pulmonary hilar lymph nodes were moderately enlarged by metastases, and the pleura revealed an interlacing grayish-white network of lymph channels filled with tumor cells which appeared to spread out from the pulmonary hilus. Many pinpoint to pinhead sized nodules were found within the parenchyma of the lung.

Of the four cases presented, only one conforms with the picture of pure lymphatic dissemination that has been stressed by certain French writers. In this case metastases from a sigmoid adenocarcinoma greatly enlarged the mediastinal lymph nodes and caused a definite carcinomatous lymphangitis of the lungs without any vascular alterations. In the remaining three cases, the presence of tumor cells in the perivascular lymphatics called forth a marked increase in the adventitial tissue and an intimal fibrous hyperplasia in many of the smaller arteries and the arterioles. Varying degrees of arterial obliteration were produced, often with complete closure of the lumen. In part the intimal response may be ascribed to invasion of the adventitia and the media by scirrhus carcinoma. In other arteries, even after serial sections had been made, no such invasion was found, and the intimal response may in part have been the result of some humoral or direct mechanical stimulus exerted by the presence of tumor cells in the lymphatic channels.

Additional cause for the narrowing of the pulmonary arterial bed was seen in the apposition of a platelet thrombus or of carcinoma cells on a hyperplastic intima, which resulted in either a partial or a total obliteration of the vessel.

In this study the findings would indicate that the obliterating endarteritis was mainly the result of lymphangitis carcinomatosa and not, as M. B. Schmidt believed, principally the result of multiple carcinomatous embolization to the pulmonary arteries.

AORTIC STENOSIS: A DIFFERENTIAL STUDY BETWEEN CALCIFIED BICUSPID VALVES OF CONGENITAL AND INFLAMMATORY ORIGIN. MAX TRUBEK and LOUIS F. BISHOP, JR.

MAX TRUBEK: Most cases of aortic stenosis may be etiologically grouped into three classes: 1. Cases of infectious origin, including those of true rheumatism, other types of infection with "rheumatic" changes and healed bacterial endocarditis. 2. Arteriosclerotic or degenerative lesions without previous inflammation. 3. Congenitally defective cusps with subsequent calcification.

After healing, fusion and calcification, it is often increasingly difficult to decide on gross examination whether one is dealing with an old inflammatory process or with a defective valve of the bicuspid variety with subsequent calcification.

The chief basis for distinction is the relationship of the origin of the annulus fibrosus to the aortic elastic media at the ridge or raphe dividing the conjoint valve.

Mönckeberg (1904) showed the architecture of the aortic cusps and, using differential stains for elastic and connective tissue, described the annulus fibrosus and its changing relationships to the aortic media at the commissures and within the cusps in normal valves. Lewis and Grant (1923) have provided a method for the microscopic identification of a congenital raphe and a fused commissure ridge by serial sections stained for elastic tissue. The contribution of Gross and Kugel (1931) established the normal architecture of each cusp and showed the contiguous relationships so that any cusp can be identified on microscopic section.

Proper reference to Mönckeberg's description of the normal aortic valve has been neglected in recent years. For the first time in such a study he used the Weigert elastica and van Gieson stains. He recognized that as the commissure is approached there is a reversal of the relationships of the annulus fibrosus to the aortic elastic media. The media seems to withdraw inward and the fibrous annulus to advance superficially from beneath the aortic elastica layer, so that at the commissure it lies superficially and extends into the cusp at its fibrous layer. The wedge-shaped junction, at first directed from the left below to the right above, becomes horizontal and then takes the opposite direction at the commissure, from the right below to the left above.

By the method described by Lewis and Grant it was possible to differentiate a congenital raphe or a fused commissure ridge in aortic valves with advanced calcification and stenosis. At the congenital raphe the normal relationships for the center of the cusp are maintained; the reversal does not occur.

In one case the presence of associated cardiovascular anomalies, coarctation of the aorta and patent ductus arteriosus, could not be taken as presumptive evidence for a congenital defect underlying the calcified aortic cusps; microscopic sections through the ridge in the combined cusp showed a fused commissure of inflammatory origin.

In one case of bacterial endocarditis the apparently normal commissural relationship at the raphe, dividing the conjoint cusps, in the absence of any inflammatory reaction and without the characteristic gross appearance of a congenital bicuspid valve, may merely have represented an abortive attempt to form a commissure. This finding and the high position of the raphe would seem to indicate a relatively later arrest in the development from the bulbus cordis thickening than occurs in the low, smooth raphe which can satisfactorily be identified on gross examination.

LOUIS F. BISHOP, JR.: One of the first recorded observations on the differential study of bicuspid aortic valves was that of Paget (1844), who wrote: ". . . in the majority of cases in which only two valves have been found in the aorta or pulmonary artery, those valves have been diseased, and often extremely diseased."

Thomas Peacock (1853) in his book, "Malformations of the Human Heart," wrote as follows: "In by far the most frequent form of malformation of the semilunar valves there are two segments, and the deficiency is apparently due to the adhesion of the contiguous sides of two of the original three valves and the atrophy of the corresponding angle of attachment."

Sir William Osler has stated the gross criteria for distinguishing the bicuspid valve of congenital origin: "The free border was usually straight, oftentimes curled, and in no instance was there any nodular thickening indicative of corpus Arantii. The attached border presented, from the ventricular aspect, either the normal contour of a semilunar valve, or, more commonly, a shallow groove, indicative of the junction of two cusps. The aortic side of the valve presented in all the cases a more or less distinct raphe, dividing or indicating a division into two sinuses. The sinuses of Valsalva, thus incompletely marked, were usually of equal size." These gross criteria are exceedingly important and can be used in the majority of cases.

There are some cases, as shown in this study, in which these gross criteria are decidedly insufficient. The difficulty in deciding this point in one case of advanced aortic stenosis with an apparently bicuspid valve led me to take this specimen to Dr. Maude E. Abbott in Montreal. She told me that a histologic study of these cases was necessary and stimulated us to do this work. This has been done by Lewis and Grant in a series of cases of bacterial endocarditis. At the present time, this is as far as one can go in the differential study.

THE USE, SIGNIFICANCE AND INTERPRETATION OF SILVER IMPREGNATIONS IN PATHOLOGY. NATHAN CHANDLER ROOT.

Silver impregnation is not a formidable laboratory method, and successful impregnations may be carried out by a college sophomore without any previous training if directions are carefully followed. The method has been slow in gaining ground in general use, owing to the fondness of pathologists for the simpler, hematoxylin-eosin technic or similar stains. Although Ranvier instituted silver impregnation in the early sixties, it was not till 1900, when Bielschowsky and Simarro began working with ammoniacal silver impregnations, that the technic began to develop. Since that time Bielschowsky and Ramon y Cajal and their followers have devised many methods for as many purposes. The fact that blocks of tissue or frozen sections were alone available held back progress, but Maresch and his successors gradually perfected methods in which paraffin sections gave good results in all but nerve tissue, and even that is now yielding to treatment, although the results are as yet not entirely successful.

The chemistry of the technic depends on attaching silver ions to certain "silver centers" in fixed tissue and then developing these with a reducing agent so that the silver is rendered black. Most methods replace the silver with gold, by means of gold chloride, which may be intensified by the Laidlaw method, using oxalic acid or a combination of this with formaldehyde. The exact chemistry of the technic is poorly understood, for nothing is known about the "silver centers." It is doubtful if they are very similar to the subsalts produced by exposure to light in the photographic plate, although the analogy has often been stressed. There are two general groups of silver salts used in impregnations: silver nitrate, which requires a strong reducer to develop it, and silver diamino salts, which are readily reduced by formaldehyde. The color effects in silver impregnation and the tissue components that become impregnated depend on: (a) the fixation used; (b) the pretreatment with alkaline or acid baths, mordants, etc.; (c) the type of silver solution used; (d) the type of toning employed, and (e) the use or omission of intensification.

Silver impregnation may be used as a general, routine stain; it brings out differences in connective tissue and bone, striae in skeletal muscle, certain micro-organisms (*Leishmania*), spermatozoa and other delicate structures, such as mitotic figures. It may be specifically used for micro-organisms, connective tissue (reticulum especially), various components of the nervous system (neurites, neuroglia, etc.), specific argentaffin granules or other granules, such as melanin, certain lipins and lime salts.

Interpretation depends on familiarity with the results of given methods of impregnation, and must be worked out by experience; there is no short cut to interpreting all impregnations. The acquisition of such experience is not a difficult matter, however, and may be materially hastened by the use of and comparison with other familiar stains.

Cleanliness in the technic is a prime factor for success, and the use of distilled water is almost invariably indicated, unless specifically contraindicated in the directions for impregnation. In those methods in which good and bad results occur in the same group of sections, it is well to make enough sections at a time to insure a reasonably large number of satisfactory slides; this refers chiefly to work on frozen sections of the central nervous system, which is notoriously capricious. When using most of the impregnations designed to bring out connective tissue or

muscle striae or general impregnations, the results are constant and usually satisfactory. The technic can be used in a routine way, just as one employs the old-fashioned hematoxylin-eosin method.

DISCUSSION

GEORGE F. LAIDLAW: Dr. Foot has long been a crusader for the use of silver in the pathologic laboratory, and I wish him all success. I am glad to acknowledge the benefit that I myself have derived from Dr. Foot's writings. Silver is one of the most remarkable of histologic reagents. There are probably four or five histologists in this city using silver, and there ought to be forty. Throughout the country there are perhaps forty using it, and there should be four hundred. In our own work we have formulated certain principles. The first is that the fixative determines the result. If one uses the right fixative, one can stain specifically any desired part of the tissue. One can stain the basic substance and leave the cells out, or stain the cells and leave the basic substance out; or one can stain the cell bodies and not the nuclei, or stain the nuclei and not the cell bodies. It is all determined by the fixing fluid.

Another thing that we have learned is that long silver technics are dirty. For neurites we follow the Gros-Bielschowsky method, and we have cut the time down to two minutes. Frozen sections are put in silver nitrate for two minutes, in formaldehyde for two minutes and in ammoniacal silver for two minutes, making six minutes in all.

Dr. Foot spoke of the liberal use of distilled water between the steps. This may apply to some technics, but in staining neurites by the Gros-Bielschowsky method we fear distilled water as the devil fears holy water. We believe that water extracts something from the tissue that is essential to the reaction. We even hesitate to renew the formaldehyde solution in which the tissue was fixed, fearing to lose something important. When we cut the sections, we drop them back into the same formaldehyde in which the tissue was fixed, and leave them there until ready for staining. Between the formaldehyde and the silver nitrate, we rinse the sections in distilled water for the shortest time possible, a few seconds only, so that they carry some formaldehyde over into the nitrate. Then we rinse them no more. The sections carry the silver nitrate over into the reducing formaldehyde, and some of the reducing formaldehyde over into the ammoniacal silver. I have tried mixing the three fluids together, but this did not work well. Cajal advised dropping some nitrate into the reducing formaldehyde to make the nerve fibers come out blacker.

One could discuss this subject for a long time without exhausting it. I believe that the distinguished author of the paper will agree with me that the surface of silver staining has scarcely been scratched and that there is no more fruitful field today for the ambitious young pathologist than the study of silver staining in pathologic histology.

ALFRED PLAUT: I should like to ask Dr. Foot a question. When one has a formaldehyde-fixed tumor and one is doubtful whether to call it carcinoma or sarcoma, what silver method should one apply for differentiation?

PAUL KLEMPERER: I should like to ask if Dr. Foot has succeeded in impregnating the basement membrane of the glomeruli of the kidney. Dr. Foot has just touched on his controversy with Mallory and Parker in regard to the differences between the reticulum fibers and collagen fibers. I wonder if he would not give his present point of view. This question is of considerable theoretical importance, and also, as Dr. Plaut has mentioned, it is of practical value in the recognition of the very early developmental stages in certain tumors, particularly in the question of reticulum cell sarcoma and lymphosarcoma.

IRVING GRAEF: I should like to ask if the silver stains have been reliable enough for the specific identification of fibrinoid degeneration of collagen. The use of the Gram-Weigert technic has always been limited because of precipitation of dye, and we have found that the pH of the fixing fluids in general laboratory

use is extremely variable and makes the Mallory phosphotungstic acid-hematoxylin method variable in its results. We have tried to use one of Dr. Foot's variants of the silver technic to determine the presence of fibrin in collagen, and have found it fairly successful, but have always had to check it up with the Weigert or the phosphotungstic acid-hematoxylin methods. I should like to ask Dr. Foot for more information on the applicability of silver methods in the identification of fibrin or fibrin-like substances.

NATHAN CHANDLER FOOT: I want to thank Dr. Laidlaw for backing me up so nobly in my crusading career, and call to his attention that in connection with the use of distilled water, I said "except when specified." Of course in such methods as that of Rogers it is suicidal to use any distilled water between the formaldehyde and the impregnating solution, but I was thinking in more general terms when I mentioned the value of distilled water between the steps; for instance, in impregnation of connective tissue it is imperative to get clean results.

Another point which Dr. Laidlaw brought out was the fascinating game of juggling with these things. In using variants of almost the same method, by alternating the different steps of one of these four processes, the steps of fixation and impregnation, and the developing and toning, one can get all sorts of combinations, so that if one method does not work, another will. I do not expect any one, after he becomes expert in the use of silver impregnation, to use any specific method. He will probably use his own.

The surface of the subject is indeed only scratched, and I do not think that we can make our scratches much deeper until we can get a little further along in the chemistry of the technic and understand more clearly what we are doing. There are a great many of the steps in our work which we do not know about, and if we could only get to understand them, it would make a great difference.

In reply to Dr. Plaut's question, the differentiation between sarcoma and carcinoma, I have found this as a general rule satisfactory with silver methods, in that the reticulum of the stroma of a carcinoma usually stops in a wall at the basement membrane, or it is only in those parts of the slide where the carcinoma cells have become broken up that the reticulum penetrates. On the other hand, in reticulo-endothelial sarcomas a dense network of reticulum fibers runs all through the tumor. I have demonstrated that certain tumors which were supposed to be carcinomatous—one case in the thyroid I am thinking of especially—were really reticulo-endothelial in origin, because of this dense network, which ran through and among all the cells. One may see other tumors which one is sure are reticulo-endothelial, but in which one cannot demonstrate any reticulum; in this difficulty, one is thrown back on another hypothesis—that the tumor may be muscular or neurogenic—and then other methods of staining must be used.

I was asked which method we use for connective tissue; I shall have to be immodest and say that we use the "Foot and Foot" method, which my daughter and I worked out. We have a number of variants, but time prevents my giving all the steps. I shall be glad to send an outline of the particular method we use to any one who wishes it; unfortunately our reprints are exhausted.

In reply to Dr. Klemperer's question concerning the glomeruli of the kidney, we can demonstrate the capsule of the glomeruli, but interestingly and amusingly, we can seldom if ever demonstrate any reticulum in the glomerulus itself. Once in a while, particularly in rabbits, we may demonstrate it, but in human tissue it seldom comes out.

In regard to the question about reticulin and collagen, that, after all, is a matter of hair-splitting. It seems to me that reticulin and collagen are intimately related, but there may be some slight chemical difference between the two, as was thought by Siegfried, who did the original analytic work. He found a different empirical formula for the two substances. On impregnation with silver under certain conditions, one can see reticulin as a black substance and collagen as a red one, and then one may find them overlapping or running into one another. Reticulin or collagen may therefore be a form of coating on some indifferent sort of a fiber. There are numerous indifferent fibers in the body which one cannot

impregnate. I have noticed this in several instances, and it is possible that collagen and reticulin may be either a coating or a substance which fills the fiber, like starch in linen. The substances are sufficiently different from each other to react differently to silver. In using the method just mentioned for general impregnation, if one employs a tannate variant, collagen and reticulin both come out red; if one does not use it, the reticulin comes out black, whereas the collagen comes out red. I do not think that this proves whether the two are the same or not. My belief that they are different was based on a smelly piece of work that I did a long time ago, in which a number of spleens and lungs were digested with pancreatin, the reticulin was reprecipitated, and an attempt was made to isolate it. I isolated something which assayed very close to the Siegfried formula and which I could impregnate with silver. It was presumably brought down in a series of chemical reactions after the collagen had been removed, and for that reason I thought that it was different from collagen. Guyon and Nageotte attacked my views in a paper that I could not fully comprehend (it was so complicatedly physicochemical that it left me gasping). There was a good deal of talk about differences of interfaces and surface tensions, which would explain the differences in the black and red impregnation.

As to fibrin, I have had practically no success in impregnating fibrin with silver, and for that reason I have always done just what Dr. Graef who asked about it does: I have fallen back on the phosphotungstic acid-hematoxylin or Gram-Weigert stain to demonstrate fibrin.

In working out the development of reticulin in tubercles, it was important to find out whether reticulin developed from the fibrin in the tubercle. By making a series of stains with silver and phosphotungstic acid, I demonstrated that reticulin did not develop from fibrin. Silver methods are worthless for impregnating fibrin.

BUFFALO PATHOLOGICAL SOCIETY

Regular Meeting, April 29, 1933

KORNEL TERPLAN, *President, in the Chair*

PNEUMONIA IN NEW-BORN INFANTS. MARGARET WARWICK.

In a series of 258 consecutive autopsies on infants dying during the first ten days of life or stillborn, 18 were so macerated that satisfactory microscopic sections of the lungs could not be obtained. This left 240 which were examined and analyzed. Forty-six infants, or 19.5 per cent, showed pneumonia. Two of these, however, had atresia of the esophagus, and repeated aspirations of food had caused a massive pneumonia; another was born of a mother who was critically ill with lobar pneumonia. These 3 were therefore omitted, and a study was made of 43, or 17 per cent.

Of these 10 were stillborn, 8 lived less than twelve hours and 6 lived between one and two days. In 24, or 56 per cent, pneumonia must therefore have developed in utero. Also, 2 were of only 5 months' gestation, showing that pneumonia can develop long before birth. About half of the infants, i. e., 20, or 46.5 per cent, had no other pathologic lesions; without microscopic sections, these would be called cases of atelectasis. Twenty-one, or 50 per cent, showed traumatic lesions, and 2, or 4.8 per cent, showed congenital lesions.

Only 11 infants, or 25.6 per cent, were born by spontaneous delivery; in all the other cases there was interference of various kinds. Three infants were delivered by cesarean section, abdominal in 2 cases and vaginal in 1. The series included many abnormal positions. Many of the infants were larger than usual, while a few were very small. These abnormalities of position and delivery sug-

gest that there may have been asphyxia owing to a variety of causes, and this may have caused an aspiration of amniotic fluid which may or may not have been infected with pathogenic organisms.

Amniotic fluid is a frequent finding in the lungs of infants who die during or shortly after birth. Some of the various constituents of amniotic fluid were found in 175, or 73 per cent, of the 240 infants; among the 43 with pneumonia, it was present in 37, or 86 per cent. The material consisted of fat, cornified epithelium, fluid and masses of bile salts in various ratios, and was usually found in the midst of the area showing the exudation of leukocytes.

All the lungs were stained by Gram's method, and in 11 instances, or 25.5 per cent, showed bacteria. There is much difference of opinion about the etiology of pneumonia. The majority of observers think that it is caused by bacteria which have entered the amniotic fluid by some route, usually by premature rupture of the membranes. In only 5, or 12 per cent, of this series did the rupture of the membranes occur long enough before birth to have caused this chain of events. In 63 per cent this period was less than one day; in the others it was not known. Furthermore, the 3 infants delivered by cesarean section could not have been thus infected.

Atelectasis is a frequent accompaniment of pneumonia. While atelectasis is frequently recognized, the underlying pneumonia is not. Many have observed that atelectatic lungs are frequent sites of pneumonia. In this series, there were large areas of atelectasis in 20, or 46.5 per cent, small areas in 11, or 28 per cent, and none in 11, or 25.6 per cent. The foreign material and exudate were frequently found in the center of atelectatic areas.

The majority of observers think that pneumonia in the new-born is caused by bacteria, but the conclusion from this study is that it is frequently, if not always, caused by the chemical or mechanical irritation of the aspirated amniotic fluid. Chemical irritants can cause acute inflammation and exudation in other parts of the body. Winternitz found that pneumonia could be produced by dilute acid, and Pierson by iodized oil. It occurs in cases in which there is no evidence of the entrance of pathogenic organisms. Also, many of these infants had handicaps of various kinds associated with size, position and difficult delivery which may have lowered their resistance and made them easier prey to either bacterial or chemical invasion of the lungs. It is possible that this pneumonia is caused by either bacteria or chemicals or both. At any rate, the pneumonia of new-born infants is a definite entity and should receive more attention from obstetricians and pediatricians. It may cause death directly by exudation or indirectly by preventing proper aeration of the lungs.

MALIGNANT HEPATOMA IN A YOUNG WOMAN. MARGARET WARWICK.

A woman, 20 years of age, was admitted to the Millard Fillmore Hospital on Feb. 19, 1933, complaining of loss of weight and strength and a growing tumor in the abdomen. The illness began in January, 1930, when the patient was pregnant about four months. A cramplike pain in the left upper quadrant of the abdomen was first noted on walking or other exertion. Following delivery the patient never regained her former strength. There was a loss of 30 pounds (13.6 Kg.) in weight. Physical examination revealed distention of the abdomen by a large irregular mass, about the size of a grape-fruit, under the left costal margin. This mass was fixed but not tender or painful. Roentgen examination gave negative results. The hemoglobin content was 55 per cent, the red cell count 3,170,000 and the white blood count 6,450, with 75 per cent neutrophils and 25 per cent lymphocytes. The blood sugar was 100 mg., and the urea nitrogen, 14 mg. The Wassermann reaction was negative. A laparotomy on Feb. 27, 1933, showed a large tumor in the left lobe of the liver, which was increased in size. A diagnosis of malignant hepatoma was made at biopsy. Postoperatively, the patient progressively lost strength and weight. She died on March 1.

At autopsy the liver was found to be greatly enlarged, especially the left lobe (weight, 2,475 Gm.). In the left lobe was a large white tumor mass with numerous areas of necrosis and extravasated blood. This was covered by a thin layer of tissue, so that it was not visible from the anterior surface. Numerous tumor nodules of a similar nature, varying from 1 to 3 cm. in diameter, were present in both lobes. Tributary lymph nodes were greatly enlarged and contained tumor tissue identical with that in the liver. Also present were recent bacterial endocarditis, multiple infarcts of the spleen and a small persistent thymus.

Microscopically, the tumor consisted of large atypical cells with pale vesicular nuclei and numerous mitotic figures. These embryonic cells resembled liver cells with typical cord formation. Large areas of necrosis were seen.

MENINGITIS IN A DIABETIC PATIENT: VARIATIONS IN THE COMPOSITION OF THE SPINAL FLUID. ROGER S. HUBBARD and BYRON D. BOWEN.

Specimens of blood and spinal fluid taken simultaneously from a patient with meningitis due to type III pneumococcus, secondary to a chronic infection of the ear, were studied. The first were taken eight hours after the first symptoms of the acute condition were noticed and four hours after coma, nondiabetic in type, developed, and the others at intervals as shown in the table. All showed marked turbidity owing to the large number of cells present. The patient died fourteen hours after the last specimen was obtained.

Determinations on the Blood and Spinal Fluid

Date	Time	Whole Blood		Spinal Fluid	
		Sugar, per Cent	Sodium Chloride, per Cent	Sugar,* per Cent	Sodium Chloride, per Cent
April 17	12 m.	0.368	0.414	0.055	0.648
April 17	4 p.m.	0.256†	0.007
April 19	12 m.	0.740	0.462	0.280	0.688

* These results are corrected for nondextrose reducing substances, determined after short incubation with a high concentration of washed yeast cells.

† Insulin was used during the preceding four hour period.

The results clearly show that dextrose may be present in typical meningitic spinal fluid in amounts roughly parallel to the concentration of sugar in the blood. Since it was proved that some dextrose was found in each specimen of spinal fluid, and therefore that this compound was always present in amounts greater than the organisms and cells could destroy, it seemed legitimate to try to determine approximately the conditions of equilibrium. The ratios between the blood and spinal fluid sugar contained in the literature vary greatly (Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Co., 1931, vol. 1), and there are no figures available with which glycolysis by a mixture of leukocytes and bacteria such as these fluids presented could be properly compared. Equations containing two unknown quantities were therefore formulated for each of the three experiments, and the probable values for the amount of sugar entering the spinal fluid and for the concentration of that substance removed by glycolysis were calculated on the assumption that both were constant throughout the period of observation. The results of these calculations agreed surprisingly well. The concentration of dextrose exposed to the glycolytic action of the cells appeared to be about 60 per cent of that in the blood, a figure which is lower than that accepted by many authorities, but which is within the range sometimes reported as normal. If this figure is accepted as correct, the calculated concentrations of dextrose destroyed were 0.166 per cent in the first experiment, 0.147 per cent in the second and 0.165 per cent in the third. Since there were a number of important factors which could not be adequately controlled—the constancy of the enzymatic potency of the cell suspension and the rate of variation of the concentration of blood sugar, for example—great emphasis cannot be laid on the particular values obtained.

The results, however, justify the statement that the dextrose in meningitic spinal fluid is controlled by definite factors, and that one of these factors is the concentration of sugar in the blood. The chloride in the spinal fluid showed a similar parallelism to the concentration in the blood. In the first sample this was 1.57 and in the last one 1.49 times as concentrated as in specimens of blood drawn simultaneously. The blood chloride was therefore an important factor in determining the concentration of chloride in the spinal fluid of this patient.

PRIMARY PULMONARY TUBERCULOUS FOCI WITHOUT CHANGES IN THE LYMPH NODES. K. TERPLAN and E. C. KOENIG.

When Kuess first described the primary tuberculous focus in children, he stated that the lymph nodes regional to the focus are always involved, sometimes to a degree altogether out of proportion to the extent of the primary lesion. In a general way Ghon confirmed Kuess' observation. Little is known concerning primary foci showing no tuberculous lesions in the lymph nodes which drain them.

Ghon was impressed by one of his cases, that of a girl, aged 5½ years, in which he could not find gross tuberculous lesions in the regional lymph nodes. In 1930 Ghon and Kudlich reported two similar cases, the first in a girl 13 years old and the second in a woman 32 years old. Serial sections from the regional lymph nodes in these two cases did not reveal any tuberculous lesions. Blumenberg also reported two instances of primary tuberculous foci with an absence of gross changes in the lymph nodes. Ghon, however, thought that the cases of Blumenberg were not convincing. In considering his own material Ghon pointed out that a small intrapulmonary node may have been overlooked grossly. Further, he suggested that special attention should be directed toward unusual cases of primary tuberculous infection without changes in the lymph nodes.

During the past six months two older children were examined who showed primary tuberculous foci in the lungs but no demonstrable lesions in the regional lymph nodes. Both of these patients gave negative tuberculin tests during life. Roentgenographic examinations of the lungs were made post mortem.

The first patient, a boy aged 12 years, dying of an abscess of the brain, showed a typical primary healed focus in the right lower lobe with a calcified nucleus on the border of which there was beginning metaplastic bone formation. A so-called specific capsule was present. The whole structure was surrounded by normal lung tissue. This focus was first discovered by means of roentgen rays. All the regional lymph nodes were examined in serial sections. With the exception of a small thickening of the reticulum in the regional lymph node of the pulmonary ligament, which was not nodular and therefore could hardly be interpreted as a healed tubercle, no tuberculous lesions were found in the lymph nodes.

The second patient, a girl aged 15 years, dying of uremia from chronic nephritis, presented a primary focus in the left upper lobe that had already been seen and felt grossly. Histologically, this focus differed from the one in the first case only in that bone formation had not yet taken place. Serial sections through all the regional lymph nodes were completely negative for tuberculosis.

In both cases thorough examination of other organs revealed no extrapulmonary tuberculosis. The age of the primary foci could not be determined with certainty.

The foregoing cases are reported for several reasons. First, they are the only cases of primary tuberculous foci in lungs with no changes in the lymph nodes in which tuberculin tests were performed during life and in which postmortem roentgen examination was made. Further, it is stressed that in adolescent children with no tuberculous changes in the lymph nodes thorough gross examination of the lungs themselves and postmortem roentgen examination are mandatory before a negative diagnosis of primary tuberculosis can be made. By this procedure additional cases of primary tuberculous foci without "complex" lymph node changes may perhaps be discovered. Finally, these cases suggest that primary tuberculous infection in late childhood, when, in general, the resistance is good, may restrict itself in rare cases to the lung tissue. Of course, the number of infecting organ-

isms may also be an important factor. It must be pointed out, however, that the two primary foci observed were not smaller than those seen in many other cases of typical changes in the regional lymph nodes.

A TENSION CAVITY IN PRIMARY PULMONARY TUBERCULOSIS IN AN INFANT. K. TERPLAN, F. KENNY and S. SANES.

The term "primary cavity" was applied to cavity formation in primary focal lesions in tuberculosis. According to Ghon's estimates small cavities are not rare. Cheesy foci the size of a hen's egg which have become sequestered and then converted into cavities are occasionally described. Exceptionally rare, however, are primary cavities in which a whole lobe is involved.

Ghon pointed out that most primary cavities have a clean wall which is sometimes rather thin. Large cavities in huge foci often show irregular borders, their walls consisting of necrotic material. Heretofore no attention has been called to a gradually increasing content of air in a cavity under certain conditions.

A colored boy, aged 10 months, died after an illness consisting of fever, vomiting and loss of weight of three months' duration. There was no tuberculosis in the family. Physical examination revealed a colored boy, fairly well developed. The frontal bosses were prominent. The cervical, axillary and inguinal nodes were palpable. A rachitic rosary was present. The right side of the chest in its lower two thirds was tympanitic. Here breath sounds were sometimes entirely absent, at other times merely suppressed. The upper right and entire left portions of the chest showed puerile breathing with many râles and rhonchi. The fingers and toes were moderately clubbed. Roentgen examination of the chest revealed areas of consolidation in both lungs resembling those of pneumonia. In the right side of the chest there was a large irregular translucent area which possessed the appearance of loops of large intestine. Barium given by mouth and colon, however, caused no filling. The Mantoux test gave negative results. The spinal fluid showed 3 cells.

This case is presented because it showed at autopsy a huge primary cavity (5.5 by 7.5 cm. in diameter) of almost the entire right lower lobe of the lung, with practically complete disappearance of the pulmonary parenchyma, but with preservation of the greater part of the bronchial tree. The right upper and middle lobes showed compression atelectasis. The mediastinum was displaced to the left. In addition, the left upper and lower lobes showed tuberculous cheesy bronchopneumonia. Small tubercles were found in the spleen and recent tuberculous erosions in Peyer's patches in the lower ileum. The right tracheobronchial and paratracheal lymph nodes were caseous, and showed on section cheesy cavities. Smears of content revealed thousands of tubercle bacilli.

A main bronchus of the second order opened into the cavity for a short distance; its peripheral extension had been entirely "melted away." The lumen of the preserved bronchus was almost totally filled with cheesy material. The cavity was markedly distended with air. Its wall and the bronchovascular framework were covered with a friable cheesy exudate. This condition, to which the term "tension pneumocavern" seems applicable, can then be explained as the result of an obstructive "valvular" action by the bronchial content. The active efforts of inspiration forced air into the cavity against the partially obstructing exudate. The passive movements of expiration were not powerful enough to force air out. Further, with destruction of pulmonary parenchyma the lower lobe had lost its elasticity. Finally, the right lower lobe was fixed to the parietal pleura by firm fibrinous adhesions.

It is interesting to note that the child did not die of acute miliary tuberculosis, but of extensive tuberculous involvement of both lungs. In other words, the course of primary tuberculosis in this case was similar to that of severe progressive pulmonary tuberculosis in adults. Only the spleen showed hematogenous tubercles; the liver and kidneys were free in examined sections. The question was raised as to the occurrence of similar tension cavities of the lungs in progressive cheesy tuberculosis of adults following partial valvelike occlusion of the bronchi.

Book Reviews

Die Lokalisationstendenz bei Metastasierung durch die Venen in der Leber. By Erik Karlmark, *Acta pathologica et microbiologica Scandinavica*, Supplementum XIII. Pp. 203. Copenhagen: Levin & Munksgaard, 1932.

Karlmark published a study in *Hygica* in 1926 and one in *Anatomischer Anzeiger* in 1927. Both deal with resorption from the gallbladder and the way it fills; the second also discusses the normal valves of the bile passages. Although these studies undoubtedly stimulated the present investigation, its chief impetus was apparently from curiosity regarding the location of secondary growths in the liver resulting from sarcoma of the gallbladder. From a few such tumors that the author was able to examine and from competent reports by others he noted that the hepatic metastases were chiefly in the quadrate lobe. This observation naturally was followed by questions concerning the normal course of the veins draining the gallbladder and the extrahepatic bile ducts. Study of these veins constitutes the main theme of the monograph. Ture Petré worked with Karlmark in demonstrating their normal anatomy. Of seventy injections into the veins of the biliary apparatus, the results of fifty-one provided material suitable for examination. The course of the veins from the gallbladder and bile ducts was charted for each of the successful preparations. The preparations were studied stereoscopically, roentgenoscopically and by reconstruction models. Translucent preparations were made after the methods of Spalteholz and others consisted simply of the veins into which pyroxilin (celloidin) was injected with the intervening tissue removed by digestion.

The usual accounts in the literature of a discharge of blood from the veins of the gallbladder and bile ducts directly into the main trunk of the portal vein or into one of its main branches were found to have no basis. Indeed, the conditions found by Karlmark and Petré are quite remarkable, for after the venous blood is collected from the gallbladder and its ducts by minute vessels which join so as to form veins of considerable size, these larger trunks pass into the liver where they split into fine branches which empty into small radicles of the hepatic veins. There are consequently *retia mirabilia* both distally and proximally for these veins, a state of affairs comparable with the efferent arteries of the renal glomeruli, which also begin and end in capillaries. Actual union between the veins of the biliary apparatus and any portions of the portal system was found so rarely that it was regarded as an anomaly.

The number, location and course of the veins of the hepatic, cystic and common bile ducts and of the veins from the neck and the fundus of the gallbladder are described and illustrated. Names are suggested for many of the veins. A substantial portion of the value of the monograph is in the twenty beautiful full page illustrations of the veins and of a few types of disease, sarcomas of the gallbladder, for example, for which the anatomy of the biliary veins has important relations. There are also many tables in which is scheduled information concerning these forms of disease. The table for sarcomas of the gallbladder includes details of thirty tumors. Unusual consideration is shown in explaining why reports of twelve such tumors were not thought worthy of inclusion with the thirty, for each of the twelve reports is reviewed in detail with reasons for its omission. Following the table is a good résumé of the clinical and anatomic features of such neoplasms. But the relation of the venous drainage of the gallbladder and its ducts was found just as directly applicable to acute cholecystitis as to sarcomas of the gallbladder, for the abscesses in the liver secondary to cholecystitis are also found in the quadrate lobe where these veins break up and empty their blood into currents destined for the hepatic veins. These matters are also displayed in a table of thirty-two cases of postcholecystitic hepatic abscesses.

Perhaps the construction of similar tables for carcinomas primary in the gallbladder or its ducts, for hepatic abscesses that follow acute inflammation of the appendix or other places in the gastro-intestinal tract and for tumors in the liver secondary to growths primary in the spleen may be regarded as a "control experiment," for in none of these types of disease is there evidence of important relations to the biliary veins comparable to that which determines the location of lesions in the liver following acute cholecystitis or sarcomas of the gallbladder. The monograph is impressive. Indications of deliberate study, prudent conclusions and thoroughness are conspicuous everywhere. For example, in order to obtain details of one of the reports of a sarcoma of the gallbladder, a report by Cascino ultimately discarded as worthless, Karlmark personally searched the medical libraries of Parma, Pavia and Milan. Material or other aid was obtained from most of the Scandinavian institutes of pathology and from those in many other places in Europe. Among these Lemberg, Strasbourg, Vienna, Berlin, Karlsruhe, Leningrad, Parma, Göttingen, Rome and Heidelberg are mentioned. It was essential that the author have help because of the rarity of some of the diseases under examination for possibilities of relevancy to the disposition of the biliary veins.

It seems that abscesses in the liver due to appendicitis are prone to develop superficially in the dome of the right lobe or in its lateral portions and that hepatic tumors secondary to primary growths in the spleen are located chiefly in the left lobe of the liver. Calculi lodged in the neck or ducts of the gallbladder so hamper the normal flow of blood through some of the biliary veins that surgeons encounter severe bleeding when the stones are removed. Since some of the veins from the fundus of the gallbladder pass directly into the liver and, according to the discoveries announced by Karlmark, empty in hepatic veins, it is not unlikely that the postcholecystectomy bleeding which sometimes fills the abdomen and causes death may be a reversal of the current, so that blood from the liver passes into the peritoneal cavity instead of the inferior vena cava. It is indeed too early to attempt any enumeration of the modifications of present views which are likely to occur as a result of these new conceptions of the venous drainage from the gallbladder and its ducts. However, it seems safe to predict that the work will be widely read and frequently mentioned.

Manual of Veterinary Bacteriology. By Raymond A. Kelser, D.V.M., A.M., Ph.D., Major Veterinary Corps, United States Army; Officer in Charge, Veterinary Division, U. S. Army School; Member of Staff, Pathological Division, Bureau of Animal Industry, U. S. Dept. of Agriculture. Second edition. Cloth. Price, \$5.50. Pp. 524, with 93 figures. Baltimore: Williams & Wilkins Company, 1933.

This book contains a large amount of information about veterinary microbiology. "No consideration has been given to organisms not of interest in veterinary medicine." The book is divided into twelve parts. The first part discusses bacteria, their morphology, physiology and classification. The classification is that of the committee of the Society of American Bacteriologists. Part II consists of five chapters on bacteriologic methods. The third part deals with infection and immunity. The chapter on theories of infection and immunity is limited to a brief presentation of the phagocytic and humoral views, Ehrlich's hypothesis of antibody formation and action and Wright's opsonic index. Not a single reference is made to American work in this chapter. Part IV, on bacterial variation, is written by Major James S. Simmons, U. S. Army, who concludes his instructive review as follows: "From this brief discussion, it will be apparent that the bacterial dissociation covers a very broad and intricate field. While there is nothing in this newer knowledge to invalidate bacterial specificity, the fact has been established that each species has characteristics more complex than we once imagined. Many of the dissociative phenomena are imperfectly understood at the present time, and in many instances, speculation as to their exact nature and significance has led to disagreement and contention. Much remains to be learned, and undoubtedly some of our present concepts will undergo revision. However, the subject is pregnant with possibilities.

and as investigations continue and our knowledge increases, it is probable that we shall gain a clearer concept of many of the now obscure problems of bacteriology." Part V, pages 143 to 334, is probably the part of greatest interest to bacteriologists and pathologists in general as it considers in systemic detail the bacteria of veterinary infections. Part VI describes the pathogenic fungi. This part lacks references to important articles on human infections caused by some of the organisms that are described. Part VII is devoted to protozoa. The chapter on parasitic protozoa is written by Col. Charles F. Craig, now professor of tropical medicine in Tulane University. Part VIII deals with the filtrable viruses of rabies, contagious pleuropneumonia, hog cholera, foot-and-mouth disease and other important animal diseases. In this part more references to recent work would have been of value. There is a short account of "pox virus," but no detailed description of cowpox or the production of vaccine virus for human use. The remaining four parts discuss serology, hematology, preparation of veterinary biologic products and bacteriologic examination of milk and water. The presentation is clear but somewhat labored and not concise or fluent. The continuous use of the scientific names of micro-organisms when simple and familiar names would answer the purpose fully gives a stilted, pedantic effect. The illustrations are helpful but only mediocre in quality. The book is recommendable as a reliable and comprehensive source of information in regard to the micro-organisms of veterinary infections.

Studies from the Institute for Medical Research, Federated Malay States, No. 21, Kuala Lumpur: Melioidosis. By A. T. Stanton, C.M.G., M.D., F.R.C.P., Chief Medical Adviser to the Secretary of State for the Colonies; formerly Director of Government Laboratories, F.M.S.; and William Fletcher, M.D., M.R.C.P., Member, Colonial Advisory Medical Committee; formerly Director, Institute for Medical Research, F.M.S. Pp. 59, with 37 figures. London: John Bale Sons & Danielsson, Ltd., 1932.

This report deals with the glanders-like disease (melioidosis, a disease like glanders), first described by Whitmore and Krishnaswamy in Rangoon in 1912. Cases have been observed in Burma, Malaya, French Indo-China and Ceylon. The disease occurs naturally in rats, rabbits, guinea-pigs, dogs and cats. In 1913 a severe outbreak occurred in laboratory animals at Kuala Lumpur. The causative organism, *Bacillus whitmori*, is "a member of the glanders group which possesses certain peculiar physical attributes, namely motility in young cultures and a corrugated appearance on glycerine-agar." The characteristic lesions are small, irregular areas of suppuration in various organs and tissues. *B. whitmori* is present in the lesions and may be found also in the blood, urine, sputum and arachnoid fluid. It is believed that the infection usually occurs by way of the digestive tract through contaminated food. There is no evidence of direct infection from man to man or from horse to man. The report gives a well illustrated and good account of the present knowledge of melioidosis in all its aspects.

CEREBRAL ARTERIES IN RELATION TO ARTERIOSCLEROSIS

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In a recent publication¹ I described the elastic layer in the cerebral vessels of twenty-three children who varied in age from birth to 15 years. The fatal illnesses of these children were the usual diseases of childhood with the exception of tuberculous meningitis, as this disease produces a well known endarteritis of the cerebral vessels. In all the patients examined, raised areas of split elastic fibers were found before and at the branching of large vessels and of many small ones. Intermingled with the split elastic tissue of these areas were long narrow nuclei and fibers, many of which stained yellow with van Gieson's method, while a few stained red. The split elastic fibers varied in number, but the type of splitting did not appear to depend on either age or disease. The areas differed from case to case in frequency and in location. At the bifurcation of the large vessels, they generally appeared as short, low mounds on one vessel wall. At the branching of the vessels they were raised and rounded over the opening, and extended along the walls of the main vessel and branch for varying distances. They were not found at all the branches or always at the same branching. They are apparently formed between the seventh intra-uterine month and birth, since none were found in a 7 months' fetus.

Hackel² studied the elastic layer in the cerebral vessels of children, and also described the areas at the branching, but found no extensions until after the age of 20. He believed that age determined the frequency of the areas and the type of splitting of the elastic layer. Beneke³ described similar areas in the bifurcation of meningeal arteries and attributed them to pulse force.

The present study continued the examination of the elastic tissue of the vessels of the circle of Willis and their branches, by means of longitudinally cut vessels in serial, paraffin and frozen sections. The number of patients was twenty-three; twelve were between the ages of 23 and 40, four between 40 and 50, two between 50 and 60, three between 60 and 70, one between 70 and 80 and one 83 years old. The

From the Pathological Department of Buffalo General Hospital.

1. Tuthill, C. R.: *Arch. Neurol. & Psychiat.* **26**:268, 1931.

2. Hackel, W. M.: *Virchows Arch. f. path. Anat.* **266**:630, 1928.

3. Beneke, R.: *Virchows Arch. f. path. Anat.* **287**:87, 1931.

vessels were grouped according to the changes in and arising from the areas of split elastic and collagen fibers at and before the branching of the vessels.

RESULTS OF EXAMINATION

GROUP A.—*Areas of split elastic and collagen fibers at the branching of the large vessels similar to those found in childhood.*

The areas were generally found at the branching of many small and large vessels and along one vessel wall at the bifurcation of the large

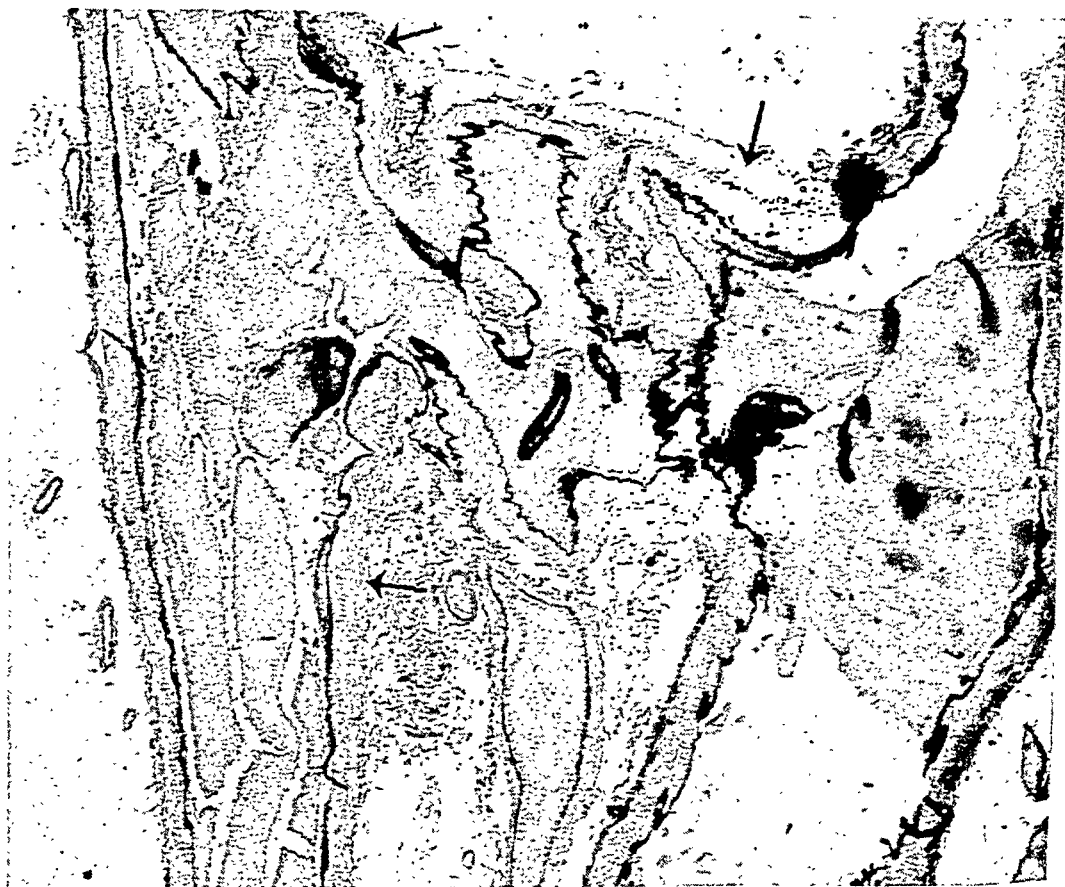


Fig. 1.—Left and right anterior cerebral arteries with the anterior communicating artery showing areas of split elastic and collagen at the branchings, in a child aged 4 months.

vessels. The extensions before the branching and into the branched vessel were short, but differed slightly in length at each branching and in each case. The height and frequency of the areas were also not constant, but were essentially similar from case to case, and were therefore as in childhood. Such variations showed no dependence on advancing age, although the ages were 23, 28, 30, 32, 33, 35, 43 and 75. Fat was not demonstrable in any of the areas at the branching or in any part of the intima. Of the six patients below the age of 40, two died

of cerebellar tumor, two from accident, one from prolonged exposure to the sun and one of pneumonia. The blood pressures, when taken, were low. The past histories and observations at necropsy were without interest.

CASE 7.—A woman, aged 43, died of a cerebellar hemorrhage as the result of a blow on the forehead. She was known to have had diabetes for ten years previous to death. Past illnesses were sinusitis, scarlet fever, pneumonia and measles. The blood pressure was 180 systolic and 100 diastolic. At necropsy were found a few atheromatous plaques only in the aorta.



Fig. 2.—The left and right anterior cerebral arteries with the anterior communicating artery in a patient aged 32, showing similar areas of split elastic and collagen fibers at the branchings.

CASE 8.—A woman of 75 entered the hospital in the last stages of primary anemia. The blood pressure was 126 systolic and 66 diastolic. At necropsy were found arteriosclerotic, contracted kidneys and a few atheromatous plaques, only in the aorta.

GROUP B.—*Solitary and generalized moderate increase in the height and extension of the areas at the branching by a growth of lipoid-free collagen fibers and split elastic fibers.*

CASE 9.—A 23 year old girl fell in the street as she came from lunch and did not regain consciousness. At necropsy a rupture of the basilar artery was found

near the branching of the posterior cerebral and communicating arteries. The gross appearance of the cerebral and other arteries presented no abnormalities; the organs were also not remarkable.

Microscopic preparations of the site of the ruptured basilar artery showed no changes in the vessel walls. On the wall of the left middle cerebral artery was found a low extension of collagen fibers from the area at the branching of the middle cerebral and internal carotid arteries. These fibers persisted to the first branching of the middle cerebral artery. In the center of this extension was a small whirl of elastic tissue surrounded by thickly set oval nuclei. This was the only pathologic finding, as the areas at the branching of the other vessels were similar to those in group A.

CASE 10.—A man, aged 44, died of chronic tuberculosis of the lungs of two and a half years' duration. The blood pressure was 100 systolic and 65 diastolic. A few atheromatous plaques were present only in the aorta.

Low extensions of split elastic and collagen fibers from the areas at the branchings ran almost the entire length of the large cerebral vessels and of many of their branches. These extensions produced a slight increase in the number of areas at the branchings.

GROUP C.—*Slight increase in the height, frequency and extensions of the areas at the branching by split elastic and collagen fibers with absorption of fat in one or several areas.*

CASE 11.—A man, aged 67, suddenly fell unconscious in the street. At necropsy a large cherry-sized ruptured aneurysm was found at the site of the branching of the left middle cerebral and anterior cerebral arteries from the internal carotid artery. The cerebral vessels were thin and smooth except for one atheromatous plaque in the basilar artery. A few atheromatous plaques were present in the aorta and slight scarring in the kidneys.

In the microscopic examination, fat was demonstrable only as free lipoid in the aforementioned area at the branching of a small artery from the basilar artery. At a few branches the increased height of the areas and their short extension were formed of collagen fibers only.

CASE 12.—A man, aged 28, fell with a hemiplegia of the right side. The blood pressure was 120 systolic and 70 diastolic. Death occurred after several days. At necropsy a ruptured walnut-sized aneurysm was found at the first branching of the left middle cerebral artery with hemorrhage into, and destruction of, the surrounding brain tissue. No pathologic findings were apparent in any other vessel or organ of the body.

Fat cells were found between the split elastic and collagen fibers in the areas at several branches from the left middle cerebral and basilar arteries.

GROUP D.—*Slightly moderate increase in the height, frequency and extension of the areas at the branching by collagen fibers, fibroblasts and fat cells in simple formation or layered over split elastic and collagen fibers.*

At a few branchings the collagen fibers, fibroblasts and fat cells formed an inner layer to the areas of split elastic and collagen fibers,



Fig. 3.—Unusual growth of collagen fibers around an elastic whirl—the only pathologic finding in all the cerebral vessels in a case of rupture of the basilar artery in a woman aged 23.



Fig. 4.—Early arteriosclerosis as shown by marked extensions of split elastic and collagen fibers from the areas at the branchings in a case of tuberculosis in a man aged 44. No absorption of fat was seen in any areas.

while at other branchings they formed the entire growth of the areas. The fibroblasts were both stellate and bipolar. The transition from the latter to fat cells was clearly shown. Lipoid was present as free fat in the outer part of the areas or in fat cells intermingled with the fibroblastic growth. Lipoid could not, however, be demonstrated in some areas of only collagen fibers. Extensions from the areas were found



Fig. 5 (case 13).—Early arteriosclerosis as shown by an increase in the height and extension of the area at the branching by collagen fibers.

on only one side of the vessel wall. They were of varying length and composed of either collagen fibers or split elastic and collagen fibers. Fat cells were occasionally found between the fibers.

CASE 13.—A woman, aged 31, died in eclampsia. At necropsy no gross lesions were found in the vessels.

CASE 14.—A man, aged 30, died in uremia. He had a past history of scarlet fever, ten years of known hypertension and renal disease. During his final stay in the hospital the blood pressure varied from 212 systolic and 128 diastolic to 258 systolic and 132 diastolic. At necropsy there were found nephrosclerosis, marked atheromatosis of the aorta and an atheromatous area at the branching of the basilar and vertebral arteries.

CASE 15.—In a man, aged 68, who had always been healthy, pain in the chest developed with dyspnea and hemoptysis. The blood pressure was 112 systolic and 84 diastolic. Death occurred in twelve days. At necropsy were found pulmonary thrombosis, arteriosclerotic shrunken kidneys and slight atheromatous changes of the aorta and of the cerebral vessels.

In the microscopic examination one area at the branching of the middle cerebral artery showed no split elastic fibers, only cholesterol crystals, hyaline fibrosis and a few fibers of collagen as an inner layer. The other areas were similar to those in cases 13 and 14, while the extensions were formed of split elastic and collagen fibers without lipid.

GROUP E.—*Moderate increase in the height, frequency and extension of the areas at the branching by fibroblasts, collagen fibers and fat cells, by collagen and split elastic fibers with few fat cells, or by hyalin in simple or layered formation with split elastic and collagen fibers.*

The extensions showed a marked increase in the height and a moderate increase in the length as compared with the previous groups. The extensions were chiefly on one side and along almost the entire length of the large vessels, but were not marked in the branches.

CASE 16.—A man of 39 had a history of a primary syphilitic infection at 36 years of age, with antisyphilitic treatment for three months. Two years later he complained of shooting pains in the legs and a girdle sensation. The colloidal gold curve was tabetic. Malarial treatment was given in the hospital, with definite improvement. A few months later the building in which the patient worked collapsed, and he fell unconscious from a blow on the head. The tabetic symptoms became greatly exaggerated, with marked difficulty in walking. He entered the hospital and died three weeks later from an ascending pyelonephritis. The blood pressure during the last year averaged 140 systolic and 65 diastolic; it was 60 systolic and 40 diastolic during malarial treatment and 150 systolic and 90 diastolic on the last admission. At necropsy only the aorta showed atheromatous plaques at the branching of the vessels.

Split elastic and collagen fibers were still present in a few areas at the branchings and extensions, but as an outer layer to a growth of collagen or of fibroblasts, fat cells and collagen fibers. In the other areas and extensions were bipolar and stellate fibroblasts and collagen fibers with numerous fat cells.

CASE 17.—A man, aged 42, with a history of no previous illnesses was brought to the hospital, partially disoriented from a fall in the street. The father and mother had both died of apoplexy. The blood pressure was 175 systolic and 20 diastolic. Death occurred in ten days from bronchopneumonia. At necropsy a small rupture was found in a cherry-sized aneurysm at the bifurcation of the left middle cerebral artery. The kidneys were not remarkable. Both the aorta and the cerebral vessels showed slight atherosclerosis.

Collagen fibers were the chief growth in both the extensions and the areas at the branching, forming either a single layer or an inner one to split elastic and collagen fibers. A few fine elastic fibers were occasionally found in the former collagen fibers. Small amounts of lipoid were demonstrable in a few areas and extensions as small globules in collagen fibers, in bipolar fibroblasts and in some transitional forms of the fibroblasts to fat cells. In only one area at the branching had free lipoid formed from broken-down fat cells. Several areas showed a marked growth of fibroblasts, fat cells and collagen fibers.

CASE 18.—A man, aged 83, died following a gastro-enterostomy for peptic ulcer. The past history was not remarkable. The blood pressure for many years



Fig. 6 (case 17).—Similar area of split elastic and collagen fibers increased in height by collagen fibers but with absorption of fat in both parts. The media is hidden by split elastic fibers at the branching of the vessel.

averaged 120 systolic and 70 diastolic with slight temporary rises. At necropsy were found arteriosclerotic contracted kidneys and marked atherosclerosis of all vessels. Near the branching of the right anterior communicating and right cerebral arteries was found a small bean-sized thrombosed aneurysm.

Split elastic and collagen fibers with a few fat cells were found at the branching of the anterior communicating and anterior cerebral arteries. All other areas were formed of hyalin, cholesterol crystals and a few inner collagen and split elastic fibers. A few extensions were composed of split elastic and collagen

fibers; the others were formed of hyalin and some inner collagen and elastic fibers. There were also some which showed a layered formation of split elastic and collagen fibers as an outer layer with hyalin as the inner layer.

GROUP F.—*Marked increase in the height, frequency and extension of the areas at the branching by a layered growth of collagen fibers over split elastic and collagen fibers with localized absorption of fat and hyalin.*

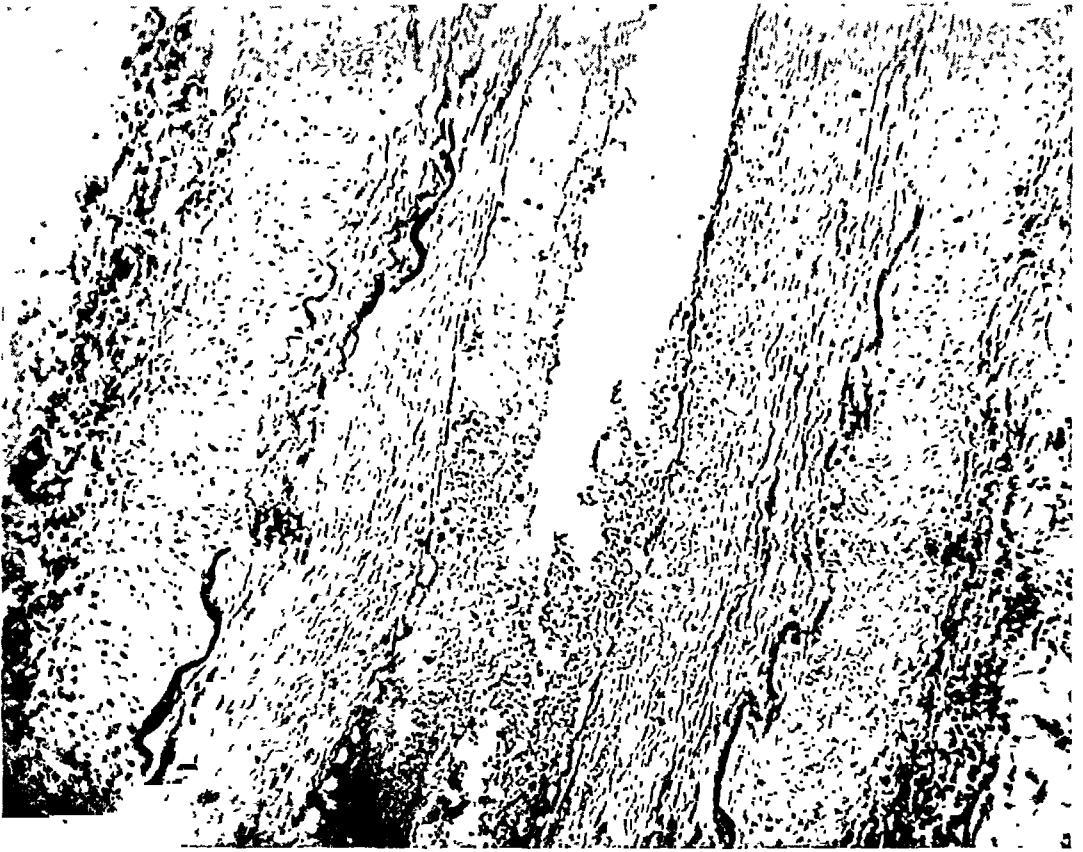


Fig. 7 (case 20).—Recurrence of arteriosclerosis as shown by an inner layer of collagen fibers over extensions of split elastic and collagen fibers. No absorption of fat occurred in either layer.

The extensions were high on both walls of the large vessels and in almost all the small branches.

CASE 19.—A man, aged 51, with a primary carcinoma of the lungs entered the hospital because of cough and swelling of the arms and hands. The blood pressure varied from 110 systolic and 80 diastolic to 115 systolic and 75 diastolic. Death occurred in a few weeks from bronchopneumonia. At necropsy metastatic carcinoma from the lungs was found in the brain. The kidneys and cerebral vessels were without gross pathologic changes. A few atheromatous plaques were present in the aorta.

The extensions and areas were either of split elastic and collagen fibers or of collagen, the latter joining the former. Hyalin was observed near one branching

as an outer layer to collagen fibers. In some areas a heavy growth of collagen formed an inner layer to split elastic and collagen fibers, while in neither layer was lipoid demonstrable. Few fat cells were found in any of the extensions or areas.

CASE 20.—A woman, aged 60, entered the hospital with an infection of the right middle ear of several weeks' duration. Past illnesses were typhoid fever, influenza, appendicitis, cystitis and two attacks of pneumonia. The infection of the middle ear became worse, and confusion, vomiting, dizziness, pain at the back of the neck and anuria developed. The blood pressure varied from 110 systolic and 60 diastolic to 130 systolic and 74 diastolic. At necropsy were found chronic otitis media, chronic osteomyelitis of the sphenoid bone, mild chronic meningitis, slight atheromatous changes of the aorta and acute glomerulonephritis. The cerebral arteries were smooth and thin.

The extensions were more marked than in case 19. Those of the larger vessels were in layered formation of split elastic and collagen fibers in the outer layer and collagen in the inner. Fat cells were occasionally observed between the fibers. A few fine elastic fibers were also found here and there in the collagen. In the small vessels were observed extensions of a moderately thick layer of split elastic and collagen fibers. A few areas at the branchings of the large vessels showed an inner layer of collagen and split elastic fibers and in their outer layers numerous fat cells, free lipoid, mitotic figures, small round nuclei with scanty protoplasm, spindle cells, cholesterol crystals and multinuclear cells. The other areas were continuous with the described extensions.

GROUP G.—*Marked increase in the height, frequency and extension of the areas in the large and small vessels by simple or layered growths in early or advanced regressive changes.*

CASE 21.—A man, aged 47, was admitted to the hospital because of the absence of knee jerks and optic atrophy. The blood pressure varied from 127 systolic and 76 diastolic to 144 systolic and 87 diastolic. There was no history of hypertension during the last three years of observation. The Wassermann reaction was negative. Death occurred suddenly. At necropsy were found small cysts of the kidneys, slight atheromatous changes of the aorta and marked atherosclerosis of the cerebral arteries. A walnut-sized thrombosed aneurysm was found at the branchings of the right internal carotid, middle cerebral, posterior communicating and anterior cerebral arteries.

In the microscopic examination of the large cerebral vessels high extension and high areas at the branching were indistinguishable in formation. Two-layered and three-layered growths predominated with a few extensions formed only of split elastic and collagen. The inner layer of the two-layered growth was formed of collagen with occasional fat cells. In some places of the outer layer there were split elastic and collagen fibers; in others, hyalin; in still others, fat cells, large cells with hemosiderin, free lipoid and spindle and multinuclear cells. The outer layer of the three-layered growth was chiefly hyalin, cholesterol crystals and calcium. The middle layer was of collagen fibers with a few fine elastic fibers, while collagen fibers only formed the inner layers. Fat cells were seldom observed in the middle or inner layers. In the small vessels were found moderately heavy extensions of split elastic and collagen fibers without lipoid. Dilated capillaries and a few light areas were observed in the media.

CASE 22.—A man, aged 52, fell in the street from a ruptured aneurysm of the basilar artery. The cerebral vessels were white, dilated and stiff. In the aorta were found syphilitic lesions.

The extensions and areas at the branchings of the large cerebral arteries were continuous, and were formed entirely of hyalin with calcium and occasional cholesterol crystals. The elastic layer was frequently absent, and no split elastic fibers were seen. Hemosiderin was demonstrable in a few cells in the outer part of the intimal growth. The capillaries of the media were dilated.



Fig. 8 (case 22).—Three-layered formation from two recurrences of arteriosclerosis. There is absorption of hyalin in the primary growth with an absence of collagen and split elastic fibers. Fine split elastic fibers are present in fat-free collagen fibers of the first recurrence. There is slight absorption of fat in the inner layer of collagen fibers of the second recurrence.

CASE 23.—A woman, aged 39, was depressed and became a secret drinker of alcohol two years prior to death. The drinking was abandoned during the last six months of life because of the onset of epileptic convulsions. The woman had never menstruated or developed secondary sexual characteristics. The uterus and adnexae were infantile. The blood pressure was increased during the last one and a half years and averaged 250 systolic and 110 diastolic. Three weeks before death a gradually increasing weakness occurred. At necropsy were found nephrosclerosis and marked atheromatous changes of the aorta and cerebral arteries.

Multiple hemorrhages, varying from the size of a pinpoint to 2 cm., were found throughout the brain. A hemorrhage the size of a hen's egg occupied almost the entire cerebellum. Other hemorrhages 2 cm. in diameter were found in the temporal and parietal cortex, putamen and pons.

All the large cerebral vessels showed high extensions of hyaline fibrosis, a few cholesterol crystals and calcium and an occasional split fiber of the elastic layer in the outer part. The smaller vessels showed varied lesions. In some of these vessels the lumen was almost occluded by split elastic and collagen fibers. In others were found clear fat cells projecting into the lumen, either alone or with a few elastic fibers pushed forward and distorted by fibroblasts and fat cells. The intima of the prearterioles of the meninges and of the brain showed split elastic and collagen fibers with or without fat cells. A few of the prearterioles were thrombosed with a hyaline change of the media and an aneurysmal widening in partial or complete rupture. Subendothelial hyalin was present in most of the arterioles of the brain substance.

Among all the cases in this series the media showed light areas beneath the intimal growth only in cases 11, 16 and 17. A hyaline change was not observed in the media.

COMMENT

Aschoff⁴ recently restated his theories of arteriosclerosis. He believes that there are two types, a presenile and a senile. The former occurs in nurslings because of a diet rich in cholesterol. In the senile type, there is first a physiologic fibrosis of the intima until the age of 40, and then a period of rest followed by fat absorption, fibrosis and absorption of hyalin and calcium. In the present series of cerebral vessels a fibrosis of the intima was not observed before the age of 40. Nor did the vessels of the six patients from 23 to 35 years of age in group A show an increase in the extension, height and frequency of the normal areas of split elastic and collagen fibers at the branching of vessels. There was a slight variation in the size of the areas in each case but not a gradual increase with age. Moreover, the areas did not show an increase with age when compared with their varied height and extension in childhood. They may even persist unchanged to the age of 75. This is contrary to the opinion of Ruehl⁵ and Hackel² who believe that a hyperplasia of the elastic layer in the cerebral vessels develops with age. The extension of collagen fibers in case 9 might be considered a hyperplasia of age, but the unusual arrangement of cells around the elastic whirl suggests a localized reaction to loosened elastic tissue. It might also be suggested that the extensions of the areas of split elastic and collagen in case 10, in a man aged 44, were likewise a physiologic hyperplasia of the elastic layer. However, the patient in case 7 was 43 and showed a complete absence of such hyper-

4. Aschoff, L.: *Beihefte z. med. Klin.* 26:1, 1930.

5. Ruehl, H.: *Veröffentl. a. d. Kriegs- u. Konstitutionspath.* 5:21, 1929.

plasia. Furthermore, such an extensive growth of split elastic and collagen was not present in a patient aged 68, in whom fat had already been absorbed in one area at the branching. It must be considered, therefore, that any increase in the height, frequency and extension of the areas of split elastic and collagen fibers at the branching of the vessels is not of physiologic but of pathologic significance.

Ceelen⁶ expressed the belief that a hyperplasia of the intima is the first change in arteriosclerosis and that the absorption of fat is secondary. On the other hand, Aschoff,⁴ Anitschkow,⁷ Hueck⁸ and Jores⁹ contended that arteriosclerosis is a disease of primary fat absorption. To support the latter theory it is necessary to show that an absorption of fat precedes an increase in the height and extensions of the areas at the branchings. Such a primary absorption of fat should therefore be evident in the vessels in group A and in those in the least advanced cases of arteriosclerosis. A primary absorption of fat could not be demonstrated. Lipoid was entirely absent from the vessels in group A. In the least advanced cases of arteriosclerosis were found free lipoid and fat cells in the areas at only a few branches in one case and in only one area of the other. Moreover, the fat-free areas at the remaining branches in these cases showed an increase in height and extension by a growth of split elastic and collagen or collagen fibers only. In the more advanced cases of arteriosclerosis were also found areas of split elastic and collagen increased in height by collagen in which was either no lipoid or but one or two fat cells. It may be argued, however, that such increases in height and extension of the areas at the branchings are the reaction to an early absorption of lipoid which has been reabsorbed. This does not appear to be probable, since lipoid-free areas of split elastic and collagen at the branchings are present in childhood. Furthermore, with the early absorption of fat in the areas, the split elastic fibers and collagen were spread apart and replaced by fat cells, while in the advanced cases the areas at the branchings no longer showed split elastic and collagen fibers, but only hyaline fibrosis, cholesterol or calcium. A destruction of split elastic and collagen was also apparent in the extensions of the areas. This was particularly demonstrated in the small vessels in case 23. In the split elastic and collagen fibers of these vessels were found numerous places in which large fat cells projected into the lumen either alone or with a few, distorted elastic fibers. The two-layered and three-layered extensions of the large vessels in

6. Ceelen, W.: *Deutsche med. Wchnschr.* **55**:1913, 1929.

7. Anitschkow, N.: *Virchows Arch. f. path. Anat.* **249**:73, 1924.

8. Hueck, W.: *München. med. Wchnschr.* **67**:535, 1920.

9. Jores, O.: *Arterien*, in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1924, vol. 2.

advanced cases were evidence of successive waves of arteriosclerosis and showed, therefore, all variations of the arteriosclerotic process from split elastic and collagen to only hyalin, cholesterol and calcium. It would seem, therefore, that in the cerebral vessels an increase in the height and extension of the areas at the branchings by split elastic and collagen or by collagen fibers precedes the absorption of fat and is the primary change of arteriosclerosis.

Since the earliest absorption of fat appeared to be in the collagen fibers and in the bipolar fibroblasts, the fibroblasts must develop from the collagen fibers. The disappearance of the collagen fibers either follows absorption of fat or is apparently due to the formation of fibroblasts and to the transition of the latter into fat cells which disintegrate and leave free lipoid. Such an absorption of fat prevents the formation of elastic fibers in a fresh growth of collagen. If, however, the absorption of fat in the latter is not immediate, split elastic fibers grow among the collagen fibers. A later absorption of fat may follow and destroy both types of fibers. There is no evidence that split elastic fibers develop after absorption of fat has destroyed the collagen fibers. Split elastic fibers are not found in the later regressive changes of hyalin and calcium, unless all the collagen fibers have not been destroyed. Split elastic fibers tend to follow the collagen fibers and are destroyed with them.

The onset and chronicity of arteriosclerosis appear to be varied. The extensions of the areas of split elastic and collagen fibers may be marked before fat is absorbed as in case 10 or slight as in the vessels in group C. There are apparently no areas of predilection at the branching in which fat is absorbed. The absorption of fat may occur in but one area as in cases 12 and 15. In the latter case, a complete hyaline change had taken place in this area before further fat was absorbed in other areas. On the other hand, the overgrowth of the areas at the branching by collagen and fibroblasts seems to denote a simultaneous hyperplasia and fat absorption and suggests, therefore, a rapid development of arteriosclerosis limited by death as in cases 13, 14 and 16. A moderately slow growth of arteriosclerosis would seem to have occurred when there is little absorption of fat, so that a penetration of the collagen by split elastic takes place as in case 17. Such moderately slow growth may be limited in extent but may recur as in case 19. The recurrences of arteriosclerosis may be wavelike with intermittances spreading through all the large and small vessels either slowly with little fat as in case 20 or with moderate absorption of fat as in case 16. In case 18 is demonstrated an almost total absence of recent new growth, while a second limited growth is almost completely hyalinized. A vigorous recurrence in only the small vessels is observed with marked fat absorption, thrombosis and rupture, while calcified lesions are present in the large vessels in case 23. The many small

hemorrhages and one large compact bleeding in the cerebellum in this last case do not confirm the belief of Boehne¹⁰ who stated that such compact bleeding is not found with the small hemorrhagic areas of uremia and hypertension. Also the clear fat cells in the small vessels were similar to those found by Rothschild and Lowenberg,¹¹ although these authors did not consider their case one of arteriosclerosis.

The present series offers no consistent etiologic factor, either in the histologic examination or in the history. A primary lesion of the media was not observed, although it is the belief of Beitzke¹² that arteriosclerosis develops from changes in the media. In marked absorption of fat the intimal lesions appear to be of granulomatous formation, as is shown by the numerous mitotic figures, the large macrophages, the small round cells, the fat cells, cholesterol, free lipid, bipolar fibroblasts and multinuclear cells. Also the change from lipid to cholesterol, hyalin and calcium is similar to the calcification of fat granulomas. In syphilitic vessels were found the same regressive changes as in arteriosclerosis. This is contrary to the opinion of Jakob¹³ who believed that both syphilis and arteriosclerosis might occur in the same vessel. Turnbull¹⁴ thought that syphilis produced only local manifestations of arteriosclerosis, but in this case all the large vessels were similarly affected. It is not possible to determine the influence of syphilis on the vessels in the case of tabes. A toxicity from disturbed renal function might be considered in five cases. In only two cases was there a possible predisposition to arteriosclerosis shown by a family history of apoplexy.

The divergence of the ages in groups of similar lesions does not suggest that arteriosclerosis is a disease of old age but that it occurs at any time. In group C, the ages are 28 and 67; in group B, 23 and 44; in group D, 30, 31 and 68; in group E, 39, 42 and 83; in group F, 51 and 69, and in group G, containing the most severe cases, the ages are 47, 52 and 39.

The lesions of arteriosclerosis must be determined microscopically, since it is only the free lipid or advanced regressive changes which are visible macroscopically.

Moschowitz¹⁵ and Dietrich¹⁶ believe that arteriosclerosis is due to the effect of intravascular pressure. Moschowitz cited as proof the

10. Boehne, C.: *Beitr. z. path. Anat. u. z. allg. Path.* **86**:566, 1932.

11. Rothschild, D., and Lowenberg, K.: *Arch. Neurol. & Psychiat.* **26**:993, 1931.

12. Beitzke, H.: *Virchows Arch. f. path. Anat.* **267**:116, 1928.

13. Jakob, A.: *Spezielle Histopathologie des Grosshirns*, in Aschaffenburg: *Handbuch der Psychiatrie*, Leipzig, Franz Deuticke, 1929, vol. 11.

14. Turnbull, H. M.: *Quart. J. Med.* **8**:201, 1915.

15. Moschowitz, E.: *Virchows Arch. f. path. Anat.* **283**:282, 1932.

16. Dietrich, K.: *Virchows Arch. f. path. Anat.* **275**:452, 1929.

development of arteriosclerosis in cases of increased pulmonary pressure, as in mitral stenosis. Steinberg¹⁷ examined the pulmonary arteries of many patients and denied the influence of intravascular pressure in the production of pulmonary arteriosclerosis. Blood pressure was not an apparent cause of the vascular lesions in this series. In case 14 hypertension was of ten years' duration, but the marked fibroblastic growth indicated a recent onset. Hypertension was known to have been present for one and a half years in the last and most severe case, but there was also a family history of apoplexy, disturbed renal and endocrine functions and alcoholism.

The early experiments of Anitschow,⁷ in which he was able to produce an absorption of fat in the intima of the aorta of rabbits by cholesterol feeding, suggested to many investigators a relation of diet and lipoid metabolism to arteriosclerosis. Raab¹⁸ recently studied the diets of people in various parts of the world. He came to the conclusion that hypertension and arteriosclerosis are less frequent in countries in which the diet is low in animal fat and vitamin D content. Eskimos of Labrador are one of these groups. A relation of disturbed cholesterol metabolism to arteriosclerosis was also suggested by Aschoff⁴ and Anitschkow.⁷ The only patient with diabetes in my series showed no arteriosclerosis of the cerebral vessels, although diabetes was known to have been present for ten years, with a blood sugar content of 175 mg. and a blood pressure of 180 systolic and 100 diastolic.

Moreover, a relation of disturbed cholesterol metabolism to arteriosclerosis is not apparent in persons with xanthomatosis, in whom the blood cholesterol content is generally high. In the 26 year old patient of Chiari¹⁹ the duration of the disease was eight years, but only a few yellow plaques were present in the aorta. Chester²⁰ recently reported a case in a man, aged 28, who showed no arteriosclerosis, although the disease was of eighteen months' duration. Arteriosclerosis was observed in two other patients with xanthomatosis by the same author.²¹ In one patient, aged 44, there was also found degeneration of the posterior columns of the cord; in the other, aged 69, hypertension was present. Herzenberg²² reported fat in the endothelium of the cerebral capillaries in a child with xanthomatosis. This fat was probably not in the endothelium but in the cells of the vessel walls as was observed by Ighenti.²³ In the reports of cases of Niemann-Pick disease, arteriosclerosis was not mentioned, although fat was demonstrable in the

17. Steinberg, U.: Beitr. z. path. Anat. u. allg. Path. **22**:307, 1927.

18. Raab, W.: Med. Klin. **28**:487, 1932.

19. Chiari, H.: Ergebn. d. allg. Path. u. path. Anat. **24**:316, 1931

20. Chester, W.: Virchows Arch. f. path. Anat. **279**:561, 1930-1931.

21. Chester, W., and Kugel, V. H.: Arch. Path. **14**:595, 1932.

22. Herzenberg, H.: Virchows Arch. f. path. Anat. **269**:614, 1928.

23. Ighenti, W. K.: Virchows Arch. f. path. Anat. **282**:585, 1931.

cells of the vessel walls. The absorption of hemosiderin in the intima in two cases of thrombosed aneurysms, is evidence that substances are taken up from the blood by intimal macrophages. The amount of hemosiderin was very small, although in one case the duration of the aneurysm was three years.

It is suggested that a relation of the volume of blood to the narrowing of the lumen of the vessel may exist. Also a mechanical influence may cause the growth of the areas of split elastic and collagen fibers at the branching of the vessels. It seems possible that the areas are developed to lead a sufficient quantity of blood from the main blood stream into the branches; therefore, as the volume of blood decreases the areas must enlarge. It would appear that the absorption of fat in the hyperplastic areas is similar to the absorption of fat in other hyperplastic growths, such as tumors. This conclusion is suggested from the observation that in only a few of the presented cases did absorption of fat occur in almost all parts of the intimal growth, and that these few cases were those of most rapid growth. Furthermore, the absence of a generalized absorption of fat and the presence of a localized fat absorption in the other cases do not offer proof of a theory of general metabolic disturbance as the cause of absorption of fat. Absorption of fat must therefore be due to localized changes in the hyperplastic intimal growth.

CONCLUSIONS

At the branching of the large, and of many small, cerebral vessels are found areas of split elastic and collagen fibers which are present from birth and may remain unchanged through adult life. The onset of arteriosclerosis is an increase in the height and extension of these areas by collagen. Unless absorption of fat accompanies this growth of collagen, the areas are penetrated by split elastic fibers. The absorption of fat may be localized in only one hyperplastic area at the branching and in any part of such an area. Fat makes its first appearance in small globules in the fibers of collagen and in the bipolar fibroblasts. From the latter are produced fat cells. A granulomatous formation occurs in a marked absorption of fat and cholesterol. In any absorption of fat, the collagen fibers are destroyed and also the elastic fibers, if present. Free lipid accumulates from the destruction of the fat cells, and this is followed by absorption of hyalin, cholesterol and calcium.

Arteriosclerosis may be rapid, slow or recurrent. Absorption of fat is marked in rapid growth and slight in slow growth. Recurrences may be of either rapid or slow growth and localized in the large or small vessels.

Hypertension, disease, diet, volume of blood, lipid metabolism, disturbed renal function and syphilis were considered in relation to arte-

riosclerosis. Neither age nor the wear and tear of vessels are an etiologic factor.

Macroscopic examination discloses arteriosclerosis only when there are either advanced regressive changes or a large amount of free lipoid from broken-down fat cells.

Lesions of the media are apparently secondary to the changes in the intima.

It is suggested that the primary hyperplasia of the areas at the branching is dependent on the volume of blood and that absorption of fat occurs as in tumor formations.

PNEUMONIA DUE TO FRIEDLÄNDER'S BACILLUS

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Recent authors have confirmed Weichselbaum's¹ postulate that lobar pneumonia in a small percentage of cases is caused by Friedländer's bacilli in pure culture. The relatively frequent presence of members of the *Bacillus mucosus-capsulatus* group in the otherwise apparently normal upper respiratory tract² makes the finding of these organisms in sputum insufficient to establish them as the cause of pneumonia. Cases of pneumonia in which cultures of the blood or of the lung showed Friedländer's bacillus have been reported by Comba,³ Béco,⁴ Philippi,⁵ Apelt,⁶ Cole,^{2d} Belk⁷ and Sweany and his co-workers.⁸ Fränkel,⁹ Cole^{2d} and Cecil, Baldwin and Larsen¹⁰ noted the rarity of such cases, and the latter two gave the incidence as about four per thousand cases of pneumonia.

I found a pure growth of Friedländer's bacillus in cultures of the blood in five cases and in cultures of the lung in one case. These cases form the basis of this report. They were discovered among 204 consecutive autopsies, but there was no suggestion of an epidemic such as that reported by Zander.¹¹ In all six cases the course was acute, unlike that described by Letulle and Bezançon,¹² Westenmark and Berglund,¹³

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1. Weichselbaum, A.: *Med. Jahrb.* **82**:483, 1886.
2. (a) Etienne, G.: *Arch. de méd. expér. et d'anat. path.* **7**:124, 1895. (b) Howard, W. T., Jr.: *Philadelphia M. J.* **1**:336, 1898. (c) Dunn, C. H., and Hammond, J.: *Interstate M. J.* **22**:1133, 1915. (d) Cole, R.: *New York State J. Med.* **19**:253, 1919.
3. Comba: *Jahresb. ü. d. Fortschr. d. path. Microorg.* **12**:101, 1896.
4. Béco, L.: *Rev. de méd.* **19**:385 and 461, 1899.
5. Philippi, E.: *München. med. Wchnschr.* **49**:1884, 1902.
6. Apelt, F.: *München. med. Wchnschr.* **55**:833, 1908.
7. Belk, W. P.: *J. Infect. Dis.* **38**:115, 1926.
8. Sweany, H. C.; Stadnichenko, A., and Henrichsen, K. J.: *Arch. Int. Med.* **47**:565, 1931.
9. Fränkel, A.: *Ztschr. f. klin. Med.* **10**:401, 1886.
10. Cecil, R. L.; Baldwin, H. S., and Larsen, N. P.: *Arch. Int. Med.* **40**:253, 1927.
11. Zander, A.: *Deutsche med. Wchnschr.* **45**:1180, 1919.
12. Letulle, M., and Bezançon, F.: *Ann. de méd.* **12**:1, 1922.
13. Westenmark, N., and Berglund, N.: *Acta radiol.* **7**:626, 1926.

Brulé and his co-workers,¹⁴ Collins and Kornblum,¹⁵ and Sweany, Standnichenko and Henrichsen.⁸ All occurred in men between the ages of 38 and 55. Two were Negroes, and four were white men. Three gave a history of alcoholism and three a history of chronic infections of the respiratory tract. The maximum duration of acute symptoms was ten days.

BACTERIOLOGY

Friedländer's bacillus is identified by the hospital bacteriologist, Dr. George W. Wheeler, as a nonmotile, gram-negative bacillus with a large, easily stained capsule, which forms large, moist, semitranslucent, mucinous colonies when cultured on agar. It produces acid and gas in dextrose and usually in saccharose; it causes little or no fermentation of lactose; it does not produce indol; it gives rise to slight acidity in milk, without coagulation; it does not liquefy gelatin. The organism produces a rounded, mucinous surface growth.

PATHOLOGIC ANATOMY

A lobular involvement has been described by Comba,³ Stühlern,¹⁶ the Mallorys,¹⁷ Sisson and Thompson,¹⁸ Westenmark and Berglund,¹³ Belk⁷ (one case), Brulé and his co-workers¹⁴ and Collins and Kornblum.¹⁵ On the other hand, Friedländer,¹⁹ Béco,⁴ Philippi,⁵ Apelt,⁶ Mosny and Pruvost,²⁰ Belk⁷ (four cases) and Fremmel, Henrichsen and Sweany²¹ have reported cases of lobar distribution. The diagnosis made at autopsy in four of the present series of cases was lobar pneumonia and in the fifth case, lobular pneumonia. In the sixth case, lobar pneumonia was shown in one lobe and lobular pneumonia in another.

Cross-section of the involved lobe in two cases showed a fairly uniform appearance, except that the periphery was grayer and the central

14. Brulé, M.; Huguenin, R., and Foulon, P.: *Ann. d'anat. path.* **4**:889, 1927. Brulé, M.; Huguenin, R., and Gilbert-Dreyfus: *Bull. et mém. Soc. méd. d. hôp. de Paris* **51**:1370, 1927.

15. Collins, L. H., and Kornblum, K.: *Arch. Int. Med.* **43**:351, 1929.

16. Stühlern, V. R.: *Centralbl. f. Bakt. (Abt. 1)* **36**:493, 1904.

17. Mallory, F. B.: *The Principles of Pathologic Histology*, Philadelphia, W. B. Saunders Company, 1914, p. 157. Mallory, T. R.: *New England J. Med.* **199**:196, 1928.

18. Sisson, W. R., and Thompson, C. B.: *Am. J. M. Sc.* **150**:713, 1915.

19. Friedländer, C.: *Virchows Arch. f. path. Anat.* **87**:319, 1882.

20. Mosny and Pruvost, P.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **35**:395, 1913.

21. Fremmel, F.; Henrichsen, K. J., and Sweany, H. C.: *Ann. Int. Med.* **5**:886, 1932.

parts of the lobe, hemorrhagic. Others ²² have reported this previously. The lobe was notably increased in density and consolidated, but showed some evidence that this consolidation represented a secondary confluence of previously separate areas of pneumonia. On section, large amounts of mucinous material oozed out as if the contents were under pressure, but the lobe in half of the cases showed also an indistinct granulation (Cordier ^{22b}).

A great majority of authors have noted destruction of the alveolar walls in pneumonia of this type ²³ which may lead to necrosis or abscess formation,²⁴ but Lord ²⁵ denied that this occurs. In my series there was beginning cavitation or abscess formation in cases 4 and 5; many of the septums in the lungs in other cases were notably edematous.

The number of organisms in the pulmonary vesicles is often enormous.^{24b} The bacilli are both extracellular and intracellular. Fibrin is usually present in small amounts,²⁶ but figure 1 shows it traversing an interalveolar lacuna.²⁷

A preponderance of polymorphonuclear cells has been noted in the pulmonary alveoli by many authors,²⁸ while others have found equal numbers of the two types ²⁹ or mononuclear preponderance.³⁰ The duration of the disease and the blood count in my four cases with predominant mononuclears were as follows: Case 1, five days; 6,800 white blood cells, with 80 per cent polymorphonuclears, 16 per cent lymphocytes and 0 mononuclears. Case 2, eight days; 1,800 white blood cells, with 43 per cent polymorphonuclears, 33 per cent lymphocytes and 24 per cent mononuclears. Case 3, two days; 6,500 white blood cells, with 88 per cent polymorphonuclears, 10 per cent lymphocytes and 0 mononuclears. Case 6, three days; blood count not done.

In the other two cases, in which polymorphonuclears were predominant but many large mononuclears also present, the duration of the dis-

22. (a) Smith, W. H.: J. Boston Soc. M. Sc. **2**:174, 1897-1898. (b) Cordier, V.; Badolle, A., and Brissaud, H.: Lyon méd. **118**:817, 1912. (c) Rosenkranz, K.: Thèse de Paris, 1912.

23. Thiroloix, M.: Bull. et mém. Soc. anat. de Paris **72**:152, 1897. Apelt.⁶ Belk.⁷ Stühlern.¹⁶ Kornblum, K.: Pennsylvania M. J. **33**:312, 1930.

24. (a) Toenniessen, E.: München. med. Wchnschr. **58**:2608, 1911. (b) Lemierre, A., and Léon-Kindberg: Paris méd. **1**:67, 1925. (c) Belk.⁷ (d) Sweany et al.⁸ (e) Westenmark and Berglund.¹³ (f) Mosny and Pruvost.²⁰

25. Lord, F. T.: Disease of Bronchi, Lungs and Pleura, Philadelphia, Lea & Febiger, 1925, p. 368.

26. Kokawa, I.: Deutsches Arch. f. klin. Med. **80**:39, 1904.

27. Miller, W. S.: J. Exper. Med. **42**:779, 1925.

28. Gouget, A., and Moreau, R.: Bull. et mém. Soc. méd. d. hôp. de Paris **34**:296, 1912. Sweany et al.⁸ Mallory, F. B.¹⁷

29. Bensley, E. H.: Canad. M. A. J. **26**:681, 1932.

30. Brinckerhoff, W. D., and Thompson, R. L.: Rep. Boston City Hosp. **12**: 149, 1901. Belk.⁷ Fremmel et al.²¹

ease and the blood count were as follows: Case 4, ten days; 4,400 white blood cells, with 83 per cent polymorphonuclears, 16 per cent lymphocytes and 1 per cent mononuclears. Case 5, from four to seven days; 13,000 white blood cells, with 89 per cent polymorphonuclears.

Figures 1, 2 and 4 illustrate the type of mononuclear cells found. Lord,²⁵ Lauche³¹ and others expressed the belief that these intra-alveolar phagocytes represent desquamated epithelial cells; Gardner and Smith,³² clasmatoocytes, and Foot,³³ monocytes from the blood. The associated finding of many monocytes in the blood (e. g., in case 2) makes me lean toward the last explanation. As an indication that the leukopenia may be more than a terminal process, the similar changes in the blood in typhoid fever, also caused by a gram-negative bacillus, may be cited. When leukopenia and fairly numerous intra-alveolar monocytes are found in pneumococcic pneumonia, they usually occur later in the disease.

REPORT OF CASES

CASE 1.—A white waiter, aged 38, had had nasal catarrh for years. There had been a chill, and there was a good deal of brownish, bloody sputum. There were signs of right lobar consolidation; the temperature was 104.2 F. Friedländer's bacilli was found in cultures of the sputum and blood, but there were no pneumococci. Death occurred on the fifth day of the disease.

At autopsy (two hours post mortem), cultures of the heart blood and sputum showed Friedländer's bacilli. Fibrinous plaques were seen on the pleura in the right axilla. The lungs were congested, the right weighing 1,625 Gm. and the left, 500 Gm. The right lower lobe was uniformly consolidated; its center was reddish and its periphery, gray. A block sank in water. Much mucinous material exuded on section, and there were fine granules on the cut surface which could not be scraped off on the knife. The spleen weighed only 100 Gm. The liver was large and fatty, weighing 1,400 Gm.

Microscopically, some of the alveoli of the right lower lobe were air-containing; others were not. The walls of many were injured, and the vessels congested. A few alveoli contained masses of fibrin (fig. 1). More of the intra-alveolar cells were mononuclear than polymorphonuclear, although clumps of the latter type were found. Short, thick, encapsulated bacilli were present in enormous numbers between the cells and in the mononuclear cells (fig. 2). No other organisms were found.

CASE 2.—A man, aged 55, a restaurant worker, with a history of alcoholism, had malaise and thoracic pain and raised blood-tinged to bloody sputum for a week before admission. The right lung showed signs of consolidation. The temperature was 103.6 F. Cultures of the blood and sputum showed Friedländer's bacilli. Death occurred seven hours after admission and eight days after the onset of symptoms.

31. Lauche, A., in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1928, vol. 3, p. 753.

32. Gardner, L. U., and Smith, D. T.: *Am. J. Path.* 3:445, 1927.

33. Foot, N. C.: *Am. J. Path.* 3:413, 1927.

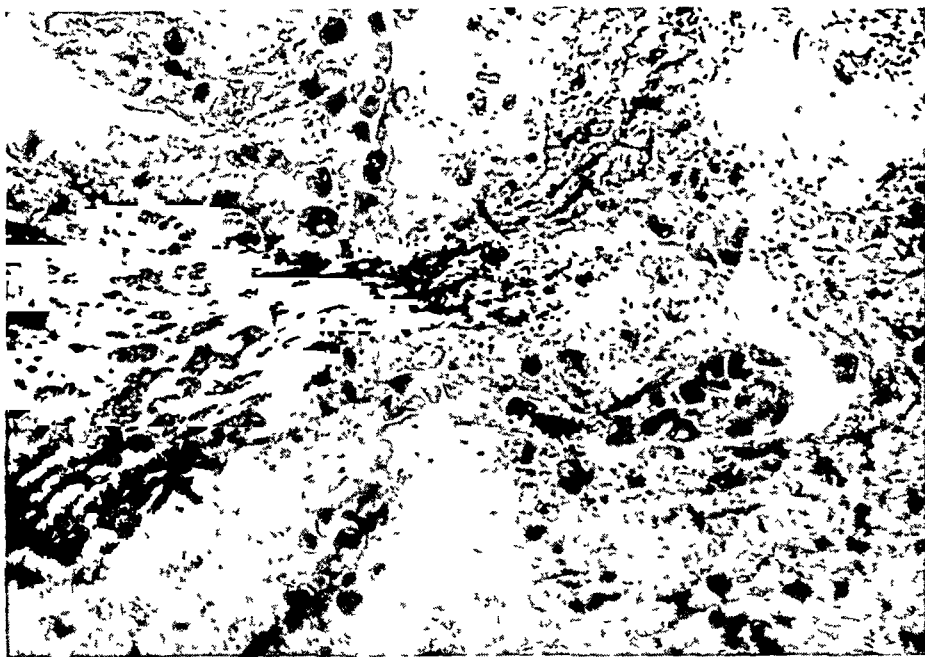


Fig. 1 (case 1).—Section showing destruction of an alveolar wall with a mass of fibrin extending from one alveolus to the next. Gram-Weigert; $\times 180$. The club-shaped mass in the right lower center represents the bulbous end of a torn alveolar septum. The innumerable small black spots represent extracellular and intracellular Friedländer's bacilli.

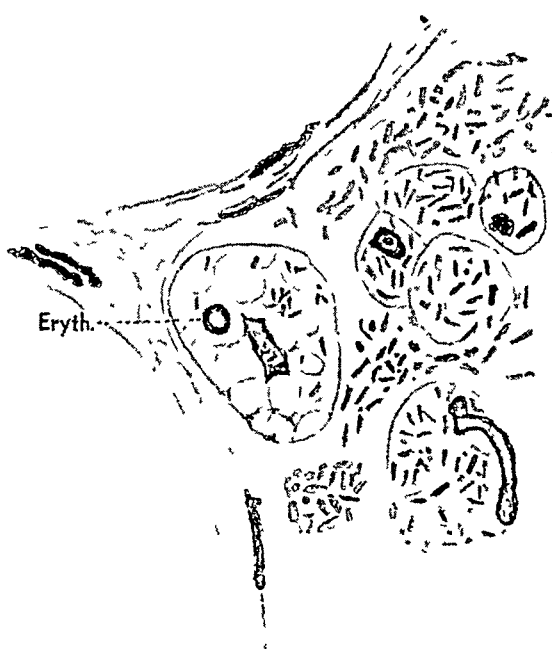


Fig. 2 (case 1).—A semidiagrammatic picture from a section of the lung showing a portion of an alveolar wall and mononuclear cells of various sizes. Gram-Weigert; $\times 500$. A red blood cell (*Eryth.*) overlies one of them. The nuclei of the epithelial cells lining the alveoli are shown.

At autopsy (seven hours post mortem), the right pleura was opaque with some fibrinous exudate. The right lung weighed 1,360 Gm.; the left, 525 Gm. The right upper lobe was of greatly increased density. Section of the lobe (fig. 3) showed complete consolidation with some suggestion of fusion of smaller foci, the central portion being red, the peripheral part gray. No air-containing alveoli were recognized and a piece sank in water. The cut surface showed some fine granulations and much mucinous material. The other lobes were congested but aerated, and the bronchi were deeply injected.



Fig. 3 (case 2) —Section of the lung two-thirds natural size showing complete consolidation of the entire lobe. The periphery is gray, and the central parts dark red.

Microscopically, some of the alveoli of the consolidated lobe (fig. 4) were opaque and somewhat translucent. Many vesicles showed a preponderance of large mononuclear cells, especially those with relatively few cells. Most of these were phagocytosing innumerable bacilli, and some of the cells were necrotic. Other alveoli showed small nests of polymorphonuclears. Many mucin-like strands were found around large numbers of encapsulated extracellular bacilli, but there was less fibrin than in case 1. Moderate destruction of the alveolar walls was present. No contaminating organisms were found in the sections. The bone marrow showed no significant histologic change.

CASE 3.—An unemployed white man of 44, a heavy drinker, without regular lodging or meals for several months, had pain in the left side of the chest, vomited and raised bloody, thin liquid sputum. There was dulness over the base of the left lung, with moist râles throughout both lungs and rigidity in both upper abdominal quadrants. The sputum showed Friedländer's bacilli and no pneumococci. Two blood cultures were negative. The patient died the day following admission, two days after the onset.

At autopsy (six hours post mortem), culture of the heart blood demonstrated Friedländer's bacilli. Old adhesions were found in both axillae. The right lung weighed 650 Gm.; the left, 1,300 Gm., and both were greatly congested. The pleural surfaces of the left were opaque. Most of the left upper lobe was consolidated. Cut sections revealed large amounts of hemorrhagic mucinous material,

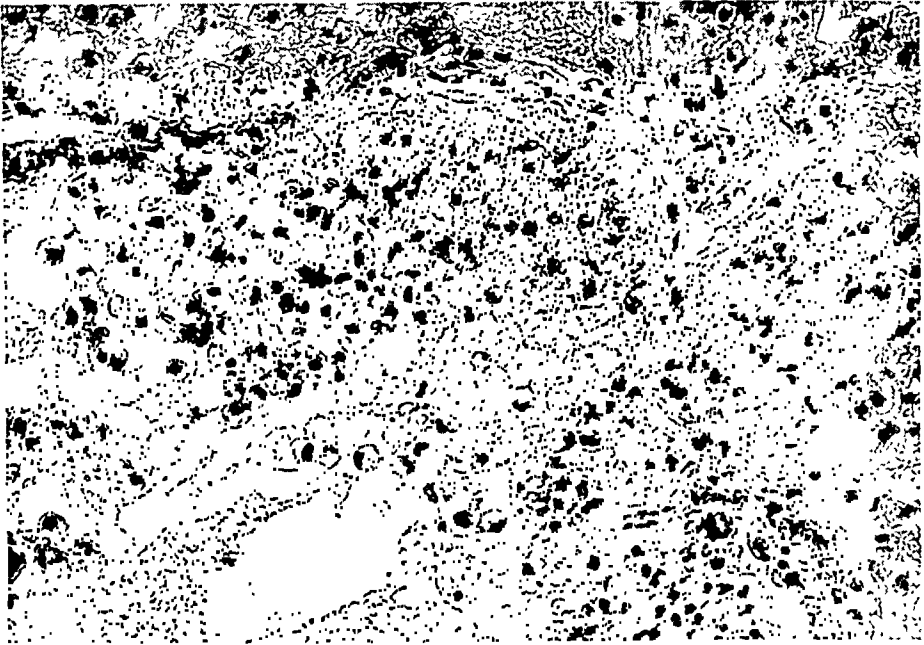


Fig. 4 (case 2).—The fine clear areas best seen at the bottom of the picture each represent an encapsulated bacillus; $\times 150$. The preponderance of large mononuclear cells is clear. The fine strands represent mucinous material.

with some scarcely recognizable fine granulations. The left lower lobe contained many firm nodular masses, chiefly from 0.5 to 2 cm. in diameter, separated from one another by small areas of air-containing pulmonary tissue. The bronchi of all of the lobes were enormously congested and filled with thick, mucopurulent material. There was a large fatty liver weighing 3,150 Gm.

Microscopic sections from both areas showed pictures similar to those in cases 1 and 2, except that there were areas in which fused necrotic cells, largely mononuclears, presented a picture resembling that of influenza. Pigment-containing mononuclear cells were present in large numbers. No organisms other than those of Friedländer morphology were identified.

CASE 4.—This case is somewhat atypical. A West Indian Negro clerk, aged 47, had had signs of accessory nasal sinus infection for many years, chronic cough and dyspnea. Râles were found at both pulmonary bases, and mottling was seen

in the roentgenograms of both pulmonary fields. There were a large heart, a blood pressure of 220 systolic and 160 diastolic and signs of nephritis. The temperature was below 100.5 F. until the fifth day after admission and around 104 F. for the last four days. Death occurred ten days after admission, and four days after the significant elevation of the temperature.

Postmortem examination (four hours after death) gave a pure growth of Friedländer's bacilli from the left pleural and pericardial cavities, each of which contained 80 cc. of pus, and from the heart blood. Numerous small consolidated areas were found in the right lower lobe, and a cavity in the right upper lobe. The right lung weighed 450 Gm. and the cut surface and bronchi were congested. The heart weighed 750 Gm., with some fibrosis. The spleen weighed only 50 Gm.

Microscopic examination showed an irregular pneumonia with marked congestion. Polymorphonuclears predominated. Bacilli of Friedländer morphology were much rarer than in the preceding cases. Cultures and examination of the sections did not reveal any other organism, and the atypical picture was thought to represent a late process rather than one due to a secondary infection.

CASE 5.—A Negro longshoreman, aged 39, had had a "cold" for six days, with rusty sputum. There was dulness in the upper part of the right side of the chest, and a roentgenogram revealed a homogeneous shadow in this region. The highest temperature was 102 F.; it decreased somewhat. Cultures of the sputum and blood showed a pure growth of Friedländer's bacillus.

At autopsy (fifty hours post mortem), friable adhesions were found around the right upper and middle lobes. These lobes were adherent to one another and were firm. Cut surfaces were shiny, with numerous small abscesses on section. The bronchi were congested and contained mucinous material. Other lobes showed marked congestion. The right lung weighed 1,325 Gm.; the left, 425 Gm.

Microscopic examination indicated that the distribution was lobar and showed polymorphonuclear and mononuclear cells in the alveoli. There were some large gram-positive bacilli, obviously postmortem invaders.

CASE 6.—An unemployed Russian Jew of 52 with a history of alcoholism had a chronic cough which was worse for three days before admission. Culture of the blood showed no bacterial growth, but culture of the sputum showed Friedländer's bacilli.

Autopsy disclosed consolidation of the right upper and lower lobes with gross and microscopic findings as in cases 1 and 2. The right lung weighed 2,000 Gm.; the left, 500 Gm. Culture of the former gave Friedländer's bacilli.

SUMMARY

Five cases of pneumonia in which the blood at autopsy contained Friedländer's bacilli and a case in which positive cultures were obtained from the lung post mortem are reported. In all the course was acute, death occurring in from two to ten days after the onset of acute symptoms. All of the patients were men between 38 and 55 years of age; four were white and two were colored. Three had a definite history of alcoholism and three a history of chronic infections of the upper respiratory tract. In four of the cases blood counts gave less than 7,000 leukocytes; in one of these less than 2,000, with 24 per cent large mononuclears.

In four of the cases there was pneumonia of lobar distribution; in one, pneumonia of the lobular type, and in one lobar distribution in one lobe and lobular in another. In five cases, a typically mucinous appearance was seen on cross-section. The pulmonary alveolar walls were more or less injured in all.

Sections of four of the lungs (cases 1, 2, 3 and 6) showed enormous numbers of bacilli in the pulmonary alveoli, while fewer bacilli were found in the other two. Large mononuclear cells in great numbers were the predominating intra-alveolar cell in these four cases, with polymorphonuclears in lesser numbers. The proportions were reversed in the other two cases. The mononuclear cells are believed to be monocytes.

RHABDOMYOMA OF THE UTERUS

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AND

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LOS ANGELES

INTRODUCTION

The term "rhabdomyoma" refers to tumors which present the histologic picture of striated muscle. It is not necessary to assume that the structure is identical with that seen in adult voluntary muscle, but the histology must represent a stage in the histogenesis of striated muscle. The tumors may be either benign or malignant. As with most other tumors, the degree of anaplasia corresponds relatively to the rapidity of the growth. Dewey¹ classified these growths into (1) those arising in preexisting striated muscle and (2) those arising in tissue which normally contains no striated muscle. She thought that the growths belonging in group 2 were teratomatous. The etiology of rhabdomyomas, regardless of their point of origin, remains veiled in the obscurity surrounding the causal factors of practically all malignant tumors.

The occurrence of this type of neoplasm is infrequent. In reviewing approximately eighteen thousand necropsies performed at the Philadelphia General Hospital, Cohen² reported one case of rhabdomyosarcoma, which presented generalized metastases. The bulk of the tumor was found in the region of the right kidney. Cohen's reasons for preferring the term "rhabdomyosarcoma" to "rhabdomyoma" are not given. In the last nine thousand consecutive autopsies performed at the Los Angeles County General Hospital we have found only one tumor of this type. In more than thirty thousand surgical specimens examined in this hospital, no tumor consisting of striated muscle has been found.

REVIEW OF THE LITERATURE

In the literature prior to 1903, sixty-three cases of rhabdomyoma were described. Benenati³ divided them into (1) rhabdomyomas arising in the urogenital system and (2) those arising elsewhere. There were thirty-nine cases in group 1, of which six were considered to

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1. Dewey, K. W.: Arch. Path. **3**:645, 1927.

2. Cohen, J. S.: Arch. Path. **13**:857, 1932.

3. Benenati, Ugo: Virchows Arch. f. path. Anat. **171**:418, 1903.

be primary in the uterus. In 1928, Bonnard⁴ described a pedunculated rhabdomyoma occurring in the uterus. The growth was firm, glistening and multilobular, and had extended through the walls of the uterus and had surrounded the ovaries and tubes. Ewing⁵ stated that tumors of this type occur in the uterus almost exclusively as sarcoma botryoides, Pfannenstiel.

Many theories have been advanced to explain the pathogenesis of neoplasms of this type. For practical purposes, the theories may be classified roughly into three main groups: 1. The growth represents a metaplasia of preexisting smooth muscle cells either in the uterus or from the walls of the arteries found within the organ. 2. It represents a metaplasia originating in the fibrous tissue of the organ. 3. It is a product of the ungoverned growth of misplaced embryonic cells. This last group is based largely on the Cohnheim cell rest or cell inclusion theory for tumors in general. Benenati³ supported the latter explanation by ascribing the formation of the tumor to misplaced blastomeres, basing his opinion on the fact that a large proportion of the growths are found in the urogenital system, the embryologic development of which is complex and intimately related to the development of the muscles of the trunk. Shattock⁶ stated that there are normally many striated muscle fibers surrounding the trigon of the bladder in the fetus, and that vagrant sarcoblasts from this region furnish the point of origin for the tumor. In a study of rhabdomyoma occurring in the uvula, Nicory⁷ agrees with those who advance the cell inclusion theory, but suggests that in certain cases an injury to preexisting striated muscle cells might set up an embryonic proliferation leading to the formation of a rapidly growing muscle tumor. Wolbach⁸ apparently held that the tumor arises from embryonic muscle cells; he traced its histogenesis through the following processes of differentiation: The myoblast, or embryonic muscle cell, at first a round or ovoid cell, becomes polyhedral and later fusiform. It contains clusters of paired centrioles located in the perinuclear zone. The centrioles go through a process of multiplication, and the clusters and the individual centrioles disperse. Fine fibrils appear connecting the dispersed centrioles which form the striations seen in the adult type of tissue. Accepting this explanation, Derman and Golbert⁹ felt that the so-called sarcomatous

4. Bonnard, A.: *Bull. Assoc. franç. p. l'étude du cancer* **17**:110, 1928.

5. Ewing, James: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 237.

6. Shattock, S. G.: *Proc. Roy. Soc. Med.* **3**:31, 1910.

7. Nicory, C.: *Brit. J. Surg.* **11**:218, 1923.

8. Wolbach, S. B.: *Anat. Rec.* **37**:255, 1928.

9. Derman, G. L., and Golbert, Z. W.: *Virchows Arch. f. path. Anat.* **282**: 122, 1931.

or syncytial portions of the tumor represent stages in the normal development of striated muscle.

REPORT OF CASE

History.—A Negro girl, aged 3 years, was first seen when admitted to the hospital on Oct. 4, 1931, with a history of a foul-smelling vaginal discharge of two weeks' duration. The discharge was clear and yellow at the onset, but one week later it became bloody. The patient's appetite became poor, and a mild fever appeared during the second week of the illness.

A hemorrhagic, necrotic, sloughing tumor was present in the vagina. There was a mild secondary anemia. The urine contained a trace of albumin and many bacteria. There was no ulceration or recognizable tumor in the wall of the bladder, although the right ureteral orifice could not be located and mild cystitis was present.

On exploratory operation one week later, a necrotic tumor mass filling the anterior portion of the pelvis was found. It was extraperitoneal, the bulk lying between the bladder and the uterus and extending into the broad ligaments. A specimen was taken for biopsy, and the condition was reported as embryonal tumor.

The patient was given high voltage roentgen therapy. The recovery from the exploratory operation was uneventful. She was apparently comfortable for three weeks, although the vaginal discharge persisted. At this time frequent urination developed.

The patient reentered the hospital on November 3, following the sudden onset of anuria on the preceding day. She had a fever of 101 F. (rectal), a pulse rate of 140 and a respiratory rate of 56. There was slight edema about the eyes. The abdomen was distended, and a large, firm, irregular mass extended to the region of the umbilicus. The abdomen above the mass was tympanitic. The vagina was filled with hemorrhagic, necrotic tissue. The anemia had increased, and the urine showed a marked increase in albumin.

During the ensuing six days the child was catheterized every eight hours. She became progressively drowsier and complained of severe abdominal pain. On November 9, she expired suddenly, with evidence of pulmonary edema.

Postmortem Examination.—The examination was limited to the abdomen. A firm, nodular tumor was found, which apparently arose in the anterior wall of the uterus below the uterovesical fold. The bladder was located on the upper anterior surface of the tumor and contained about 50 cc. of clear urine. The growth had infiltrated the trigon. The ureteral orifice on the left was found to lie in the tip of a polypoid mass of the neoplastic tissue. The orifice of the right ureter was not involved. Both ureters, however, were compressed as they passed through the surrounding tumor tissue and were dilated above the point of obstruction. The growth had permeated both broad ligaments in their entire extent. The entire uterus was replaced by neoplastic tissue, and the canal was distended by a necrotic, polypoid mass which had pushed through the cervix. The cut surface showed that the entire tumor was composed of firm white lobulated tissue with scattered yellow, granular striations resembling, in the gross, the ordinary fibromyoma. No metastatic deposits were found in the lymph nodes draining the pelvis or in the liver.

Microscopic Examination.—The tissue from the tumor was fixed in 10 per cent formaldehyde. Various stains, including hematoxylin and eosin, phosphotungstic

acid-hematoxylin, Mallory's and van Gieson's connective tissue stains, and Perdrau's method were tried.

The microscopic structure permitted the growth to be divided into two portions. The greater portion consisted of a well differentiated tissue resembling adult striated muscle and a less extensive portion composed of anaplastic tissue resembling fibrosarcoma. The resemblance of the embryonic tissue to fibrosarcoma, however, was only superficial, as was clearly shown after more minute examination.

The characteristic portions of the tumor when stained with hematoxylin and eosin revealed elongated cells having an acidophilic, very finely granular cytoplasm



Fig. 1.—Photomicrograph of the differentiated portion of the tumor showing the abundant fibrous connective tissue stroma. Hematoxylin and eosin stain; $\times 80$.

which contained definite cross-striations. The presence of longitudinal striations was suggested in an occasional cell. Minute study of the isotropic bands did not reveal the presence of Krause's membrane. The fibers were irregularly arranged and showed no tendency to form primary muscle bundles. The sarcolemma was apparently branched at the extremities of the fibers. The nuclei were large, hyperchromatic and centrally located; they were piled up in groups of from six to eight in one cell and showed a tendency to be rounded. Mitotic figures were rarely seen in these areas. The nucleoli numbered from one to three and were usually found immediately beneath the nuclear membrane. The surrounding collagenic fibrous tissue as demonstrated by van Gieson's stain was abundant, loosely packed and moderately vascular. There was no inflammatory infiltration.



Fig. 2.—Photomicrograph of the adult type of striated muscle cells. Hematoxylin and eosin stain; $\times 300$.

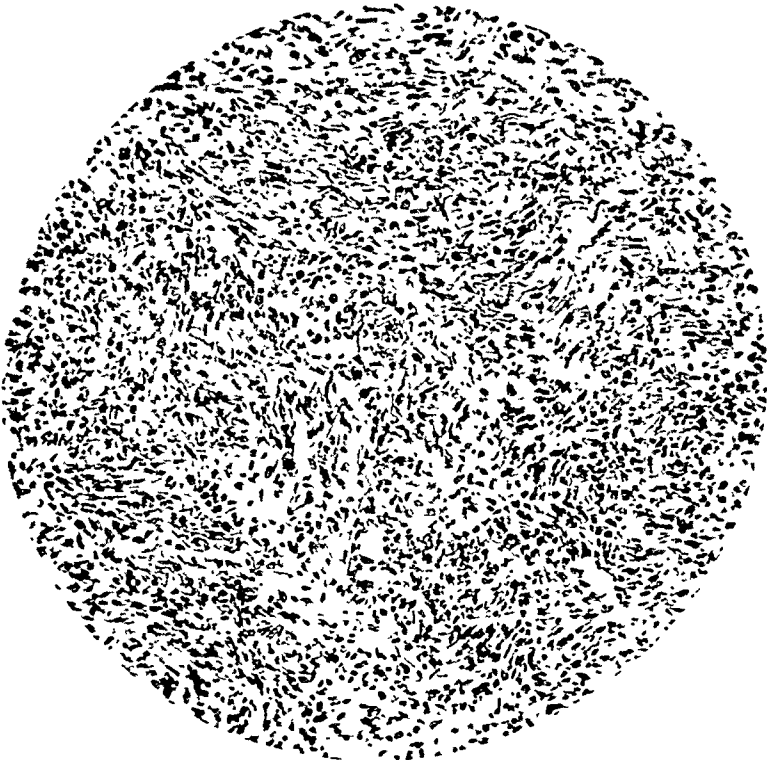


Fig. 3.—Photomicrograph of the anaplastic portion of the tumor, which resembles fibrosarcoma. Hematoxylin and eosin stain; $\times 110$.

The anaplastic tissue was more abundant in the advancing margin of the growth. No striated fibers were seen in the subserous infiltration on the wall of the bladder or in the peritoneal extension about the ovary. The anaplastic portion was characterized by its marked cellularity. The cells showed an extreme variation in size, and all degrees of variation in shape from round to fusiform. The nuclei were not definitely hyperchromatic, though they stained darker than the nuclei of the fibroblasts in the intercellular connective tissue. Mitoses were not so frequent as was expected, considering the marked cellularity and the variation in the size and the shape of the predominating cells. The nuclear chromatin was largely distributed near the nuclear membrane. The connective tissue was abundant but not dense, and supported well formed vascular channels. The tumor cells did not line these vessels, as is frequently the case in sarcoma.

COMMENT

Two essential problems are suggested by the tumor just described. The first may be briefly stated as follows: On what basis are we justified in saying that the tumor is not a spindle cell sarcoma? The second problem concerns the relationship between the cellular, anaplastic portion and the well differentiated portion containing the striated muscle tissue.

This tumor differs from the ordinary fibrosarcoma in the structure of the connective tissue stroma, the qualitative cellular appearances and the structure of the blood vessels. The stroma is more abundant than is normally seen in sarcomas showing an equal degree of activity in growth. The structure of the stroma is less dense and more edematous than is commonly found in a fibrosarcoma. The stroma contains fibroblasts which are not in any way to be confused with the tumor cells. The tumor cells vary in shape from round to oval and show a staining reaction different from that of the stroma cells. The cells are elongated with markedly acidophilic cytoplasm, and in many areas show cross-striation characteristic of muscle cells. The number of mitotic figures is surprisingly small in comparison with the morphologic variation in the cells. The blood vessels are well developed, and in no area do the tumor cells form the wall of a blood channel, as they so frequently do in sarcoma.

The problem of histogenesis presents greater difficulties than that of differentiation. The round cells of the anaplastic tissue appear to be typical myoblasts, and all stages in the development of differentiated striated muscle cells from the embryonic myoblasts can be found. We have not been able to trace the development of the striations from the paired centrioles through a dispersion process, as described by Wolbach.⁸ However, the intimate association of the anaplastic tissue with striated muscle cells in an area where voluntary muscle is not normally found suggests that both tissues are related histogenetically. The embryologic character of this voluntary muscle tissue is further indicated by the

location of the nuclei in the center of the cell rather than beneath the sarcolemma, by the clustering of the nuclei rather than their even distribution in the length of the cell and by the presence of an abundant intercellular connective tissue.

SUMMARY

1. The extreme rarity of rhabdomyomas is noted.
2. A uterine rhabdomyoma occurring in a Negress, aged 3 years, is described clinically and pathologically.
3. The histologic differentiation of the anaplastic portion of a rhabdomyoma from a sarcoma is discussed.

BUDDING FORMS (CONIDIA) IN CULTURES OF SPOROTRICHUM SCHENCKI

FRED D. WEIDMAN, M.D.

PHILADELPHIA

It is well known that in tissue, particularly pus, *Sporotrichum schencki* occurs only as budding forms; mycelia are absent. In culture, however, mycelia dominate the colony. It is true that there are reproductive bodies (conidia) which sprout abundantly from the mycelium as minute ovoid cells in smaller or larger clusters, but they are far removed morphologically and taxonomically from budding forms.

During many observations on fifteen or twenty strains of *Sporotrichum* in the Laboratory and in the classroom, the budding forms of conidia which I shall describe in this paper were confined to one strain and they occurred only sporadically in that strain. Meyer,¹ it is true, reported that he observed "blastomycetoid" cells in a fresh planting of pus containing *Sporotrichum* (from a horse) on agar, but his description was brief (only seven lines). It is conceivable that the cells had not yet become stabilized in their new saprophytic existence and retained their propensity to budding. On the other hand, it may be questioned whether the gross appearances on agar were adequate to identify the strain botanically as *Sporotrichum* in view of the atypical microscopic features that Meyer gave for it. His description would also hold for *Monilia*, since typical conidia of *Sporotrichum* were not mentioned. ("Long mycelia with typical clusters of spores were always absent. Macroscopically and microscopically these clusters appeared in every respect like yeast or *saccharomyces*.") This objection is particularly cogent in view of present-day tendencies to classify fungi on the basis of microscopic features rather than on that of the symptom complex (disease) induced or on that of the macroscopic appearance of the culture, which must have influenced Meyer in classifying his strain.

Again, Langeron² stated that yeast forms were observed in primary cultures from pus by Lutz and Splendore, as well as by Beurmann and Gougerot; the yeast forms did not persist in culture as they did in my own strain, being replaced by a mycelial type of growth.

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1. Meyer, K. F.: *J. A. M. A.* 65:579 (Aug. 14) 1915.

2. Langeron, M.: *Les sporotrichoses*, in Roger, Widai and Teissier: *Nouveau traité de médecine et de thérapeutique*, Paris, Masson & Cie, 1925, vol. 4, p. 491.

Henrici,³ too, described yeast cells in cultures of *S. schencki*, but they developed from germinating chlamydospores, not independently from the thallus, as is essential for the concept of conidia, whether of *Sporotrichum* or of any other fungus.

Budding forms were figured by Brumpt,⁴ but for a different species, *Rhinocladium* (*Sporotrichum*) *gougeroti*. They were designated "conidies-levures." So far as they are figured in his text, they extended singly from hyphae, and not from the clusters which are much more characteristic of *Sporotrichum* and which were met in the strain of *S. schencki* with which I am concerned here.

In any event, there is evidence from several independent centers that strains of *Sporotrichum* are liable on rare occasion to budding formations.

It is emphasized that both the budding and the conidial forms reported here occurred in the same environment, i. e., in culture—indeed, in the same hanging drop. By way of contrast, dimorphism within a species as it grows in a differing environment, i. e., now in pus (or other tissue) and now in culture, is well known. For example, the organism of Gilchrist's disease, *Blastomycoides dermatitidis*, exhibits budding cells in tissue (including pus), but none in culture; in culture, mycelia and conidia are formed almost exclusively. However, here again an exception has been met in which the usual type of cell was supplemented by another; Spring⁵ observed that hyphae (though abortive) were formed in the pus of an experimental mouse.

MATERIALS, METHODS AND RESULTS

The strain studied was received from the American Type Culture Collection (no. 2,615); it had been deposited by Castellani as *S. schencki* in 1920. Clinical data were not available. Obviously the strain had been repeatedly subcultured. In my hands it has comported itself like *S. schencki*, becoming black with age; however, I have not made the agglutination and other immunologic tests that were described by Davis.⁶

Budding forms were observed on one occasion in each of four contemporaneously planted hanging drop cultures 28 days old made in Sabouraud's dextrose bouillon. On a second occasion they were observed in five or six hanging drop preparations made by students in the classroom. The general architecture of the colony, with slender hyphae and

3. Henrici, A. T.: *Molds, Yeasts, and Actinomycetes*, New York, John Wiley & Sons, Inc., 1930, p. 95.

4. Brumpt, E.: *Précis de parasitologie*, ed. 3, Paris, Masson & Cie, 1922, p. 1122.

5. Spring, D.: *J. Infect. Dis.* **44**:169, 1929.

6. Davis, D. J.: *J. Infect. Dis.* **12**:140, 1913.



Fig. 1.—Colonies 2 months old; on Pennsylvania medium (a modified Sabouraud medium) at the left and on carrot at the right. The colonies are deep brown or black. The white portions on carrot medium indicate dissociation and compare with the “senile protuberances” described by Sabouraud.



Fig. 2.—Hanging drop culture 28 days old in Sabouraud's dextrose bouillon. The more normal formations appear at the bottom of the illustration, i. e., small conidia arranged in more or less trefoil clusters at tips of lateral hyphae. The closely branched arrangement at two places higher up suggests *Botrytis*.

a tendency to coremium formation, was developed according to type. As usual, conidia were abundant on a comparatively slender type of mycelium, and sprang both as individuals and in clusters from its main trunks as well as from shorter or longer conidiophore hyphae. Many conidia were typically minute and apiculate, and a few extended from denticulate formations in the hyphae, such as are the basis for the genus *Rhinocladium*, as emphasized by Langeron.

The atypical conidia were abnormal in three respects: (1) They were swollen; (2) they were spherical, and (3) many exhibited buds. In addition, the points of attachment to the parent hyphae were most



Fig. 3.—The hypha at the left shows typical *Sporotrichum* clustering (*A*) and the atypical budding forms, both formations occurring on the same hypha. At the right a few of the smaller, normal conidia which serve as controls are shown. Note the swollen state of some conidia (preparatory to budding?) and the occurrence of budding forms still attached to the parent hypha (marked by arrow). Two buds may extend from one cell.

indefinite; however, this was due to the late stage at which the preparation came under observation, at which time dehiscence is to be expected with *S. schencki*. Nevertheless, some of the budding forms could be discovered while still attached to the parent hypha (fig. 3). Usually but one bud extended from a single cell, but as many as four were sometimes discovered on special search. The question of a mixed cul-

ture did not enter since both typical conidia and budding forms could be found, although at some distance apart, *on the same hypha*. Budding forms of conidia did not occur on the dextrose-free agar of Sabouraud.

COMMENT

Genesis of the Budding Forms.—The genesis of the budding forms appeared to be the same as that for conidia, i. e., growth from the lateral walls of hyphae. Indeed, the budding forms may properly be regarded as conidia which became precociously enlarged while still attached to the parent hypha, or at least promptly after dehiscence. It is axiomatic in mycology that conidia do not germinate until dehiscence, and perhaps this restraining biologic influence, while sufficient to prevent the development of germ tubes and hyphae, was not quite adequate to prevent the minor expression of germination connoted in budding.

Once well removed from the hyphae, the budding forms gave rise to germ tubes and hyphae, as shown by the presence of both buds and hyphae, which sometimes extended from the same conidium. In no case did they originate within a hyphal segment like intercalated chlamydospores. These budding forms may be looked on as temporary fugacious forms interposed in the life cycle of a protean organism such as *S. schencki* as the result of a vicarious abnormal urge to reproduction on the part of its conidia.

Taxonomic Value of Budding.—Perhaps the outstanding message from this observation, at least in the general mycologic aspect, is a reminder that the lines are not drawn hard and fast as to the production of budding forms in species of fungi. This is illustrated in various forms, for instance, between the germination of an essentially hyphal cell like a chlamydospore and that of a quasi-budding form as exemplified in certain yeastlike cells which my associates and I⁷ recently observed in *Acrotheca* and other agents of chromoblastomycosis. Similar thoughts probably occurred to Ota⁸ when he created his "pseudoblastomycosis," including sporotrichosis and chromoblastomycosis, as well as infections with *Mycoderma*, *Scopulariopsis*, and *Coccidioides immitis*. Indeed, the bud of the blastosporinae is but a variant of the thallospore, as illustrated by Vuillemin's classification in which the blastosporinae comprise one subdivision of the thallosporales.

In addition, this experience shows that budding may exceptionally occur as a variation under comparatively uniform conditions of culture. The medical mycologist should fully realize these limitations and grant that whereas the urge to reproduce by budding is predominant in certain species under certain conditions and is a most valuable criterion in

7. Wilson, S. J.; Hulsey, Sim, and Weidman, F. D.: Arch. Dermat. & Syph. 27:107, 1933.

8. Ota, Masao: M. J. Aichi M. School 7:31, 1925.

determinative work, it is not an absolute criterion. Exceptions must be expected from time to time. When met they should be accepted only at face value and with a full appreciation of the extent of the biologic vagaries rampant among fungi.

The experience in the classroom already mentioned emphasizes this. The same strain of *Sporotrichum* was used by over fifty students; conidia developed exclusively in the hanging drops except in five or six instances. In the latter cultures there were numerous budding forms in addition to conidia.

I do not believe that the occurrence of budding forms in this strain is sufficient to indicate a new genus, or, for that matter, a new species of *Sporotrichum*. Under the influence of such varying conditions as must have arisen during repeated cultures in at least three different laboratories, it is understandable that conditions such as occur in pus were sufficiently approximated from time to time to elicit the development of budding forms without at the same time preventing the development of mycelia.

The occurrence of budding cells in culture brings *S. schencki* closer to the "yeasts." Its moist, pasty, glistening appearance in the test tube (particularly in the early days of growth), resembling that of yeast cultures, and the budding forms observed exclusively in tissue are reconcilable with Ota's impulse to include *Rhinocladium* (*Sporotrichum*) among fungi causing the condition which he calls pseudoblastomycosis.

I disclaim any intent to overemphasize the occurrence of budding cells in cultures of *S. schencki*; at most it appears to be exceptional and should not influence the previously held belief as to the differing morphology of this species in pus and culture.

Relation to Botrytis.—In figure 2 it will be observed that in addition to the clusters of conidia which occur in the form characteristic of *Sporotrichum* there are large grapelike clusters. In these the conidia are borne on compact aggregations of branches which are not a usual expression of the architecture of *Sporotrichum*. The closeness of the branching suggests *Botrytis*, although it may be objected that the lateral branches do not come off perpendicularly enough and are rather lengthy. It appears that but one instance of similar formation has been recorded in the dermatologic literature, i. e., in Benedek's⁹ *Sporotrichum lipsiense*, which was isolated from a case of dermatophytosis. Grutz criticized Benedek's determination, contending that the organism was a member of the genus *Botrytis*.

In any event, such a type of branching is sufficient to prompt attention to phylogenetic relationships with *Botrytis*, particularly since the genera *Sporotrichum* and *Botrytis* both belong to the family Botrytidae.

9. Benedek, T.: Dermat. Wchnschr. **83**:1695, 1926.

It is further in point that the botanist has already met difficulties in this section of the taxonomic field; the imperfect stage of the ascomycetic genus *Hypomyces* appears variously as forms of *Botrytis*, *Sporotrichum* or *Verticillium*.¹⁰

From this, thoughts are again turned in the direction of a vegetable source in nature for *Sporotrichum*, as *Botrytis* is such an important plant parasite (being found on horse chestnut, pine and spruce trees as well as on grape vines and lettuce, bean, geranium, dahlia, primrose, strawberry and several other plants). On lemon trees it produces gummosis.¹¹

SUMMARY

In a strain of *S. schencki*, spherical or oval budding forms occurred abundantly on the hyphae in addition to the characteristic more or less ovoid conidia. This was an exceptional phenomenon, occurring but a few times in over sixty preparations. Budding is not limited to species of fungi ordinarily classed as blastomycetes, but must be expected to emerge on occasion in other thallosporales; the occasional development of budding forms must therefore be appraised with discretion and not overemphasized taxonomically. The experience brings *S. schencki* closer to the "yeasts." The results recounted here should not modify the facts already established as to the characteristics of *S. schencki* in culture; namely, that the almost exclusive mode of reproduction is by conidia, not by budding forms. The occurrence of conidia on compact aggregations of branches may indicate affinities of *Sporotrichum* with *Botrytis*, an important parasite of a great many plants.

10. Gaumann and Dodge: *Comparative Morphology of Fungi*, New York, McGraw-Hill Book Company, Inc., 1928, p. 237.

11. Stevens, F. L.: *Plant and Soil Fungi*, New York, The Macmillan Company, 1925, p. 386.

A SUBCUTANEOUS "MIXED" TUMOR (SALIVARY GLAND TYPE) OF THE LEFT THIGH

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"Mixed" tumors containing mesoblastic and epithelial-like components occur commonly in the parotid gland, neck and oral regions, and in the urogenital viscera. The term "mixed" is used generally, although with some protest, to express this conglomeration of heterogeneous tissues. Islets of hyaline stroma resembling cartilage are usually present. The degree of mesoblastic tissue differentiation, the arrangement of the epithelial-like tissues and their combinations are not uniformly the same. There is, however, a close similarity in the tissue of the tumors arising in a certain region, such as in the salivary glands, the neck and the mouth.

Occasionally, mixed tumors resembling those of the salivary glands are found in some unusual part of the body. Kreibig,¹ in 1931, reported two such growths on the extremities. One of these occurred opposite the right shin of a man aged 38, at the junction of the upper and middle thirds of the leg. Six years before, he had had a "stone" bruise without external laceration; soon thereafter he noted a freely movable, pea-sized nodule that enlarged gradually and painlessly. It had grown rapidly for two years and was hard, sharply limited and readily enucleated. The periosteum and bone nearby showed no changes.

This firm tumor, the size of a hen's egg, was lobulated on the surfaces made by cutting. The tissues were mottled gray-white and translucent. Septums extended into the growth from the connective tissue capsule, dividing it into variably shaped lobules. The epithelial components were glandular structures, cell nests and cords. The glandular elements had a lining epithelium in two layers, of which the inner often was tall columnar. The lumens were empty or had eosin-stained masses and droplets. Among the solid cell cords were solitary, sharply circumscribed, circular masses of concentrically layered pavement cells, hornified in the center, and with keratin granules and intercellular bridges peripherally: a typical epithelial pearl. A few of these cell masses were edged by a single layer of regular cylindric cells; the centers were horni-

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From the Henry Baird Favill Laboratory of St. Luke's Hospital and the Norman Bridge Pathological Laboratory of Rush Medical College of the University of Chicago.

1. Kreibig, W.: *Frankfurt. Ztschr. f. Path.* **42**:281, 1931.

fied. The ground substance resembled cartilage. In this interpretation, however, Kreibig made some reservations because of the variable amounts of fibrillar connective tissue or elastic fibers, the variations in cell forms and the indefinite margins of the islets. He did not consider these objections significant.

The second tumor in Kreibig's report occurred on the ventral surface of the left forearm of a man aged 30. Within three years it had grown gradually into a small hard nodule. A small defect in the superficial fascia was noted in excising the nodule, but there were no changes of the bone and periosteum. There was no recurrence three years later. Histologically, the tissue resembled closely the first tumor; both were like a mixed tumor of the parotid gland.

The only other record of such growths, according to Kreibig, was by Tessmann.² This nodule, larger than a cherry, was in the subcutaneous fat dorsally near the wrist between the first and second metacarpal bones of a middle-aged woman. It had developed in four years, had the structure of a mixed tumor of the parotid and had been diagnosed chondromyxo-endothelioma.

Growths described as mixed tumors have been reported also in the subcutaneous tissues of the face³ and scalp.⁴

REPORT OF CASE

A Negress, aged 34, was admitted to St. Luke's Hospital on Jan. 3, 1933, for the excision of a mass the size of a small apple, anterolaterally on the left thigh, the lower edge being about 10 cm. above the patella. Eight years before, she had noticed a freely movable nodule as large as a pea which gradually increased to the size mentioned. It was painless but, because of its location, frequently had been traumatized. On January 4, Dr. William B. Fisk removed the tumor with a closely adherent strip of skin. The growth lay entirely in the skin and subcutaneous tissues and did not reach beyond the deep cutaneous fascia. The surgical wound healed promptly; the patient was dismissed five days after the operation. On May 25, there was no recurrence.

The encapsulated bean-shaped mass with coarsely scalloped edges was 7.5 by 5.5 cm. and 4.5 cm. thick. A strip of dark brown, wrinkled skin tapering at each end, and 8.5 by 3.5 cm., was closely adherent on one flat side. The surfaces made in bisecting the mass were tan-brown and gray, slightly translucent tissues with a few widely distributed masses of yellow fat, and were divided into three conspicuous lobules and a small less distinct lobule (fig. 1). Thin fibrous septums separated the lobules from each other. The lobules contained masses of opaque tan-gray tissue several millimeters in diameter interspersed with more translucent tan-brown tissue. The contrast between these two tissue elements was

2. Tessmann, E.: Ueber eine Mischgeschwulst in der Gegend des Handgelenks von histologischen Character der Mischtumoren der Speicheldrüsen, Inaug. Dissert., Würzburg, 1911.

3. Brunschwig, A.: Arch. Otolaryng. **13**:52, 1931.

4. Delaney, P. A.: Arch. Path. **12**:145, 1931.

more conspicuous in some of the lobules than in others. There were a few small hemorrhages. The surfaces made by cutting were moist with a small quantity of viscid fluid.

A thin slice cut from one of the surfaces made in bisecting the mass was fixed in Zenker's solution. The tissues were embedded in paraffin, sectioned and stained with hematoxylin-eosin, phosphotungstic acid-hematoxylin, Mallory's aniline blue and van Gieson's and Weigert's elastic fiber stains. Another small piece was fixed in a trinitrophenol acid-formaldehyde solution⁵ and stained according to Laidlaw's silver method.

The tissue elements were essentially of two kinds (fig. 2): masses of epithelial-like cells intermingled with stroma (islets of cartilage). The epithelial-like cells were in solid aggregates and in tubules or acini. In the solid masses they were polymorphous, about the size of cells in squamous epithelium, with an abundant acidophilic, finely granular cytoplasm and oval or round vesicular nuclei containing scattered fine and coarse chromatin granules. They were arranged compactly in

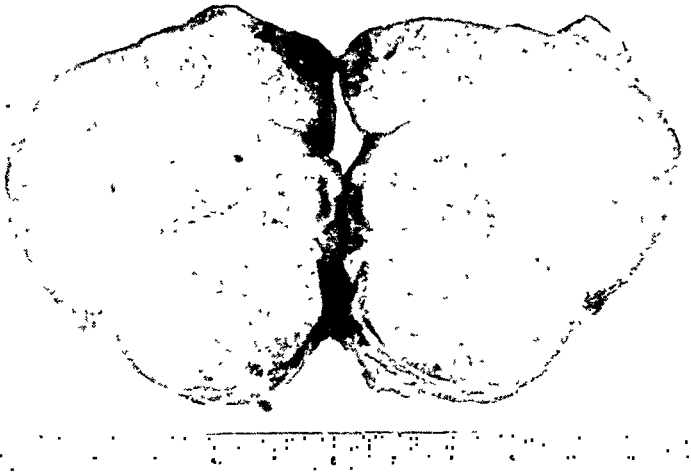


Fig. 1.—Photograph of the surfaces made in bisecting the mixed tumor of the left thigh.

mosaics, occasionally concentrically, and in a few places about round or oval masses of hyaline material not exceeding from six to eight times the long diameters of the cells. The tubular or acinar structures ranged from small ducts to the medium-sized acini of thyroid tissues. The lining cells were flattened, cuboidal or columnar epithelium, some in a single layer and others in two or possibly three layers. These tubules or acini were distinct and separate, or they were in or continuous with the compact masses of epithelial-like cells. Within their lumens were granular amorphous or colloid-like materials.

Hyaline masses resembling cartilage (fig. 3), with scalloped or roughly indented edges, formed a considerable amount of the tissues in the sections. A fibrillar, variably edematous stroma and the epithelial elements filled the interstices between them. Hyaline matrix tissues were penetrated considerably by single cells or small masses. Many large and small lacunae were in the islets of the hyaline tissue. Some of the lacunae were empty, others had a single cell or several cells

5. Solution of formaldehyde, U. S. P., 500 cc.; distilled water, 1,500 cc.; glacial acetic acid, 100 cc.; trinitrophenol to saturation point.

indistinguishable from the epithelial elements, and still others had cells angulated and like cartilage elements. Muroid degeneration, necrosis and liquefaction were marked in some sections. In the preparation stained with phosphotungstic acid-hematoxylin, the coarse stroma in the epithelial masses had the staining qualities of collagenous fibers. The cartilage-like masses had many delicate fibers which stained sharply with Weigert's elastic tissue stain but less distinctly with the Mallory aniline blue and the van Gieson stains. In preparations stained by the Laidlaw silver method, only a few of the fibers in the masses of cartilage were blackened. The interstitial tissues had many sinuous, fine and coarse reticulum fibers. The resemblance in structure of these tumor tissues to those of a mixed tumor of the parotid gland was remarkable.

An explanation of the origin of this growth on the thigh involves theories⁶ that have been proposed for mixed tumors in other parts

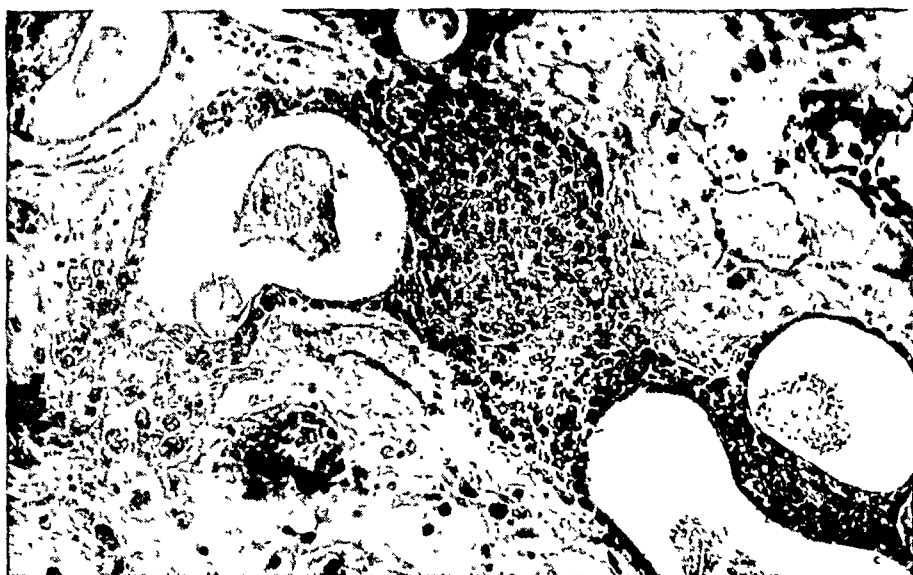


Fig. 2.—Photomicrograph illustrating the tissue elements in the mixed tumor of the left thigh, their arrangement, and the close resemblance to similar tumors of the salivary glands. Reduced from a magnification of $\times 234$.

of the body. Those suggested for the histogenesis of the so-called mixed tumors of the parotid consider them as arising from (1) connective tissue endothelium, (2) epithelium alone or (3) connective tissue and epithelium. The sponsors of the first idea regard the solid strands of cells and acinar structures in the tumors as endothelial derivatives, the cartilage arising from stroma. The proponents of the epithelial origin of the tumors consider the first mentioned tissues epithelium, and the

6. Lang, J. F.: Sogenannte Mischgeschwülste der Speicheldrüsen, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1929, vol. 5, part 2, p. 140. Kux, E.: *Virchows Arch. f. path. Anat.* **280**:175, 1931. Zymbal, W. E.: *Beitr. z. path. Anat. u. z. allg. Path.* **91**:113, 1933.

stroma portions, in particular the cartilage-like tissues, as an epithelial product. The third and, according to Kux, the simplest explanation, is the derivation of these tumors from two germ layers, fibro-epithelial tissues; hence the origin of the mucinous and cartilaginous tissues from mesoderm.

The application of these opinions to the tumor discussed involves consideration of the tissue elements from which the growth was derived. Ricker and his students, Kreibitz stated, accepted these tumors as secreting epitheliomas and assumed that epithelial derivatives of sweat glands

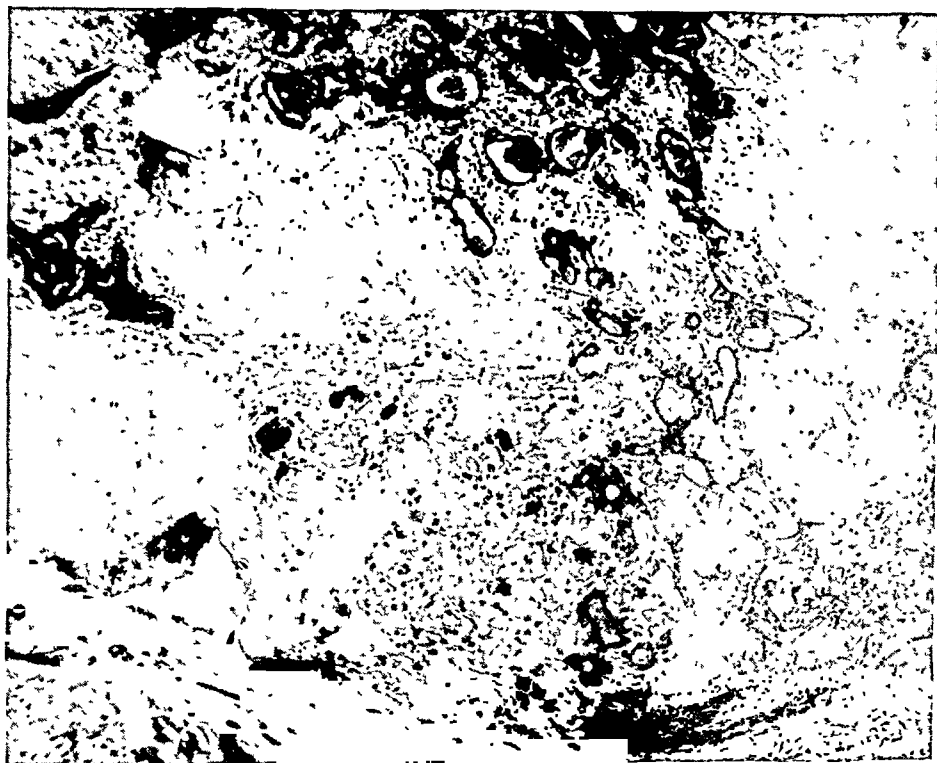


Fig. 3.—Low power photomicrograph illustrating the extensive masses of cartilage in the tumor.

may form cartilage-like and mucoïd tissues. Zymbal supported the complete epithelial derivation of the mixed tumors. The theory of an embryologic displacement of tissues, proposed by Wilms⁷ and others in explanation of mixed tumors, seems satisfactory for the growths that they considered. Although this may explain the few mixed tumors found on the extremities, the objections to such a conclusion are not readily dispelled. The proximity of the growth to the skin rather than to the deeper structures of the thigh, for example, is not correlated easily with mesenchymatous tissues containing cartilage.

7. Wilms, M.: *Die Mischgeschwülste*, Leipzig, A. Georgé, 1900.

Kistler's⁸ study of the multiple islets of cartilage in a mixed tumor of the uterus suggested a growth impulse in connective tissues, stimulating focally a differentiation into cartilage. Under such conditions the stroma of an epithelial tumor arising locally in the skin or its derivatives (sebaceous or sweat glands or hair follicles) develops a hyaline matrix resembling cartilage. Kux reviewed the statements regarding the true cartilaginous character of the hyaline tissues in these tumors. He concluded that there can be no doubt regarding the presence of cartilage in these so-called mixed tumors, but his studies did not establish whether the cartilage was heterologous, accessory or secondary, or primary. The dense network of elastic fibers in the ground substance, he stated, indicated a secondary origin because elastic fibers are typical of such accessory cartilage formations. Such a view agrees with Kistler's: the development of cartilage in fibrous stroma.

SUMMARY

A clinically benign mixed tumor grew slowly for nine years in the subcutaneous thigh tissues of a Negress. The structure of this growth resembled mixed tumors of the parotid gland.

8. Kistler, G. H.: *Am. J. Cancer* **16**:399, 1932.

NEUROMATOSIS OF THE VERMIFORM APPENDIX

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NEW ORLEANS

In 1921, Masson¹ and Maresch² reported the finding of neuromatous tumors in obliterated appendixes. At that time they believed that these growths were of the nature of amputation neuromas, because they thought that they were caused by a division of the sympathetic filaments of the mucosa by an ulcerative process or by injury to the nerves by an inflammatory process. In 1922 Schweizer³ found neuromatous structures in 40 per cent of 12 obliterated appendixes removed for chronic appendicitis and in 60 per cent of 20 obliterated appendixes obtained post mortem. He concluded that these were neurinomas of Verocay. Neurogenic appendicitis (neuromatosis) was observed 16 times by Urech⁴ in the course of the last 400 appendectomies performed in the Surgical Clinic of Lausanne. Of the 16 appendixes, 4 were removed because of acute pain; 3 of these showed no gross or microscopic evidence of inflammation, and in 1, phlegmonous appendicitis was engrafted on the neurogenic appendicitis. This case of Urech's reminds one that secondary inflammation in a neuromatous appendix is a possibility that must be thought of in the clinical diagnosis of neurogenic appendicitis. In the routine examination of a retrocecal obliterated appendix obtained at necropsy from a 70 year old woman, Barth,⁵ in 1929, observed an axial neuroma and a simultaneous proliferation of carcinoid tumor cells. Masson⁶ has recently stressed the close interrelationship between neuroma and chromo-argentaffin or carcinoid cells; he showed that the latter are always present in the growing or fully developed axial neuroma of the obliterated appendix, and that the neuromas regress and are absorbed if the argentaffin cells disappear. These

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1. Masson, P.: *Lyon chir.* **18**:281, 1921; *Compt. rend. Acad. d. sc.* **173**:262, 1921; *Congrès de médecine, Strasbourg, 1921. Compt. rend. de l'Assoc. d. anat.*, 1922, p. 217; *Neural Proliferations in the Vermiform Appendix*, in Penfield, Wilder: *Cytology and Cellular Pathology of the Nervous System*, New York, Paul B. Hoeber, Inc., 1932, vol. 3, sect. 25, p. 1095.

2. Maresch, R.: *Wien. klin. Wchnschr.* **34**:181, 1931.

3. Schweizer, P.: *Schweiz. med. Wchnschr.* **52**:1202, 1922.

4. Urech, E.: *Rev. méd. de la Suisse Rom.* **48**:425, 1928.

5. Barth, H.: *Virchows Arch. f. path. Anat.* **273**:62, 1929.

6. Masson, P.: *Am. J. Path.* **4**:181, 1928.

intranervous argentaffin cells spring by a process of budding from the epithelium of the glands of Lieberkühn and migrate out into the periglandular plexus. Masson showed that appendicular neuromas arise from the nerves of the periglandular plexus, and that they regress individually. Picard and Appelmans' ⁷ patient, a man, aged 26, complained of persistent pain in the right iliac fossa over McBurney's point but showed no muscular rigidity. Three months previously, he had a typical attack of acute appendicitis with fever. Operation revealed a neuroma, from 3 to 3.5 cm. in diameter, in the proximal half of an obliterating appendix.

In addition to the argentaffin cell neuroma just described, sympathetic neuroma and neurofibroma can occur in the appendix. The presence of ganglion cells in sympathetic neuroma (ganglioneuroma) has been reported by Oberndorfer ⁸ and by Schultz.⁹ These cells were accidentally found in the routine examination of postmortem material in Schultz' case (a man, aged 57). However, Oberndorfer's patient, a man 28 years old, was operated on for acute perforated appendicitis, and the operation revealed a primary giant growth of the appendix combined with ganglioneuromatosis of the same organ. The appendix was more than 16 cm. long. Associated with the rich number of nerve fibers, there were extraordinary huge masses of ganglion cells which were in part arranged in groups so that they could be seen macroscopically in the stained sections. The mesentery of the appendix showed typical neurofibromatosis; the body, too, was covered with tumors and showed extensive pigmentation of the skin, all typical of Recklinghausen's disease (multiple neurofibromatosis). Pick ¹⁰ believed that Oberndorfer's case was not associated with ganglioneuromatosis but with neurinomatosis. This brings up the old dispute whether these multiple tumors of nerve trunks are neurofibromatous (hence mesodermal in origin) or neurinomatous and schwannian (hence ectodermal in origin). The discussion of this dispute is only of theoretical interest and need not be taken up here. In Peritz' ¹¹ patient, a woman of 73 years, who had a sudden onset of vomiting and pain in the right lower quadrant, but no increase in temperature or in the leukocyte count, operation showed a neurinomatous tumor mass of the appendix. Schmincke ¹² described a neurinomatous formation both in the obliterating appendix and in the meso-appendix. Hoey's ¹³ patient, a man,

7. Picard, E., and Appelmans, R.: *Rev. belge sc. méd.* **1**:241, 1929.

8. Oberndorfer: *Ztschr. f. d. ges. Neurol. u. Psychiat.* **70-72**:105, 1921.

9. Schultz, A.: *Centralbl. f. allg. Path. u. path. Anat.* **33**:172, 1923.

10. Pick, L.: *Beitr. z. path. Anat. u. z. allg. Path.* **71**:560, 1922-1923.

11. Peritz, L.: *Zentralbl. f. Chir.* **57**:2475, 1930.

12. Schmincke: *Centralbl. f. allg. Path. u. path. Anat.* **33**:17, 1922.

13. Hoey, T.: *Brit. M. J.* **2**:490, 1928.

aged 47, who had Recklinghausen's disease, complained of intermittent colicky pains in the abdomen, later localizing in the right lower quadrant, where he had since felt a tender swelling. The temperature was 97 F.; the pulse rate, 72, and the respiratory rate, 20. The pathologic report was neurofibroma of the appendix.

Probably one of the first to describe this peculiar giant anomaly of the intestinal tract was Lotz,¹⁴ who studied a specimen of horse intestine, 55 cm. long, about two thirds of which was markedly thickened and of giant size so that the wall was 22 mm. thick. Meissner's plexus was truly of gigantic dimensions, containing numerous ganglion cells. The mesentery, strictly corresponding to the giant growth, showed plexiform tumor masses of the splanchnic nerve. Pick¹⁵ cleverly described this giant growth as if the intestines of a much larger giant animal had been anastomosed into the intestines of the horse. Cases of markedly enlarged appendixes reported in the American literature by Howard¹⁵ (12.5 by 8.8 cm.), Strong¹⁶ (15 by 6.3 cm.), Williams¹⁷ (10 by 3.5 cm.) and others in all probability belong to this group of giant growth and indicate that secondary inflammation may help to swell the already large appendix and give rise to acute symptoms. Lotz, Pick and Holz¹⁸ concluded that they could see no etiologic relationship between neurofibromatosis of the mesenteric nerves and the giant growth of the intestinal segment; they believed that both were coordinated congenital malformations.

Can it be that this association of giant growth of the appendix or of an intestinal segment and neurofibromatosis or their corresponding mesenteric nerves is only fortuitous? Pick and Bielschowsky¹⁹ and Winestine²⁰ reported the same case of a man, aged 60, who presented symptoms of sharp abdominal pain over variable periods, diarrhea, rectal incontinence, tenesmus and periods of obstipation. Necropsy revealed multiple neurofibromatosis of the lumbar and pelvic sympathetic nerves and adenomatous polyposis of the rectum. The topographically intimate and exact relationship between this adenomatous blastomatosis of the rectal mucosa and the neurofibromatosis of that

14. Lotz, A. C. L.: *Der partielle Riesenwuchs mit besonderer Berücksichtigung des sogenannten sekundären, eine pathologisch-anatomische Untersuchung*, Inaug. Dissert., Berlin, G. Schade, 1914.

15. Howard, W. F.: *Northwest Med.* **4**:110, 1912.

16. Strong, S. M.: *Am. J. Surg.* **28**:472, 1914.

17. Williams, C.: *Virginia M. Monthly* **52**:569, 1925.

18. Holz, H.: *Ueber fortschreitenden partiellen Riesenwuchs*, Inaug. Dissert., Frankfurt, 1919.

19. Pick, L., and Bielschowsky, M.: *Centralbl. f. allg. Path. u. path. Anat.* **33**:172, 1922-1923.

20. Winestine, F.: *J. Cancer Research* **8**:409, 1924.

particular segment of the rectal nerves was striking. Winestine concluded that there is a syntropic combination of neurofibromatosis with pure blastomatosis, paralleling the combination of neurofibromatosis and true giant growth. In a review of the literature of multiple neurofibromatosis, I²¹ found that Recklinghausen's disease is often associated with one or more types of tumors, this very multiplicity of different tumors connoting an underlying congenital defect, probably due to dysontogenetic influences.

EXAMINATION OF 195 CASES OF NEUROMATOSIS OF THE VERMIFORM APPENDIX

For this study, the 344 consecutive vermiform appendixes removed at operation and showing no evidences of acute inflammation were fixed in a diluted solution of neutral formaldehyde, U. S. P. (1:10), Zenker's fluid and a formaldehyde-trinitrophenol solution.²² Many microscopic sections, serial and otherwise, were cut from three or four different portions of the appendix and stained with hematoxylin and eosin, van Gieson's trinitrophenol-fuchsin, Mallory's phosphotungstic acid-hematoxylin,²³ Laidlaw's lithium silver,²⁴ Foot and Mènard's ammonium silver²⁵ and Masson's trichrome.⁶ A detailed study of these 344 appendixes revealed neuromatosis in 195.

Description of Neuroma.—The gross appearance of appendixes the seat of neuromatous growths is mostly normal, there being nothing characteristic to indicate the presence of such tumors. In a few cases, the distal portion of the obliterated appendix was slightly enlarged in a fusiform or bulbous manner, but other benign tumors such as carcinoids, fibroma and myoma present similar enlargements. The lumen of the majority of appendixes was partially or completely obliterated. Most of these neuromatous growths were of microscopic size. When they were large enough to be noticeable grossly, the cut surface appeared opaquely grayish-white.

For the study of microscopic sections in the identification of neuroma, the Masson trichrome stain was found to be the best. Very often minute groups of neuromatous tissue will escape detection when other staining methods are used. If the sections are properly stained, the Masson method quickly picks out and identifies the neuromas as red

21. Hosoi, K.: Arch. Surg. 22:258, 1931.

22. Formaldehyde-trinitrophenol solution is made up as follows: solution of formaldehyde, U. S. P., 500 cc.; distilled water, 1,500 cc.; glacial acetic acid, 100 cc.; trinitrophenol to saturation point.

23. Mallory, F. B., and Wright, J. H.: Pathologic Technique, ed. 8, Philadelphia, W. B. Saunders Company, 1924.

24. Laidlaw, G. F.: Arch. Path. 8:363, 1929; Am. J. Path. 5:239, 1929.

25. Foot, N. C., and Mènard, M. C.: Arch. Path. 4:211, 1927.

loosely anastomosing strands of nonmedullated nerve fibers (fig. 1) or as red islands of compact interlacing bundles in a field of deep blue, the blue representing the tinctorial reaction of the fibrofatty tissue composing the axial core of the obliterated appendix. Whenever the muscularis mucosae is intact, the neuromas are seen to lie central to it (fig. 2). Indeed, the neuroma if large enough may fill the entire

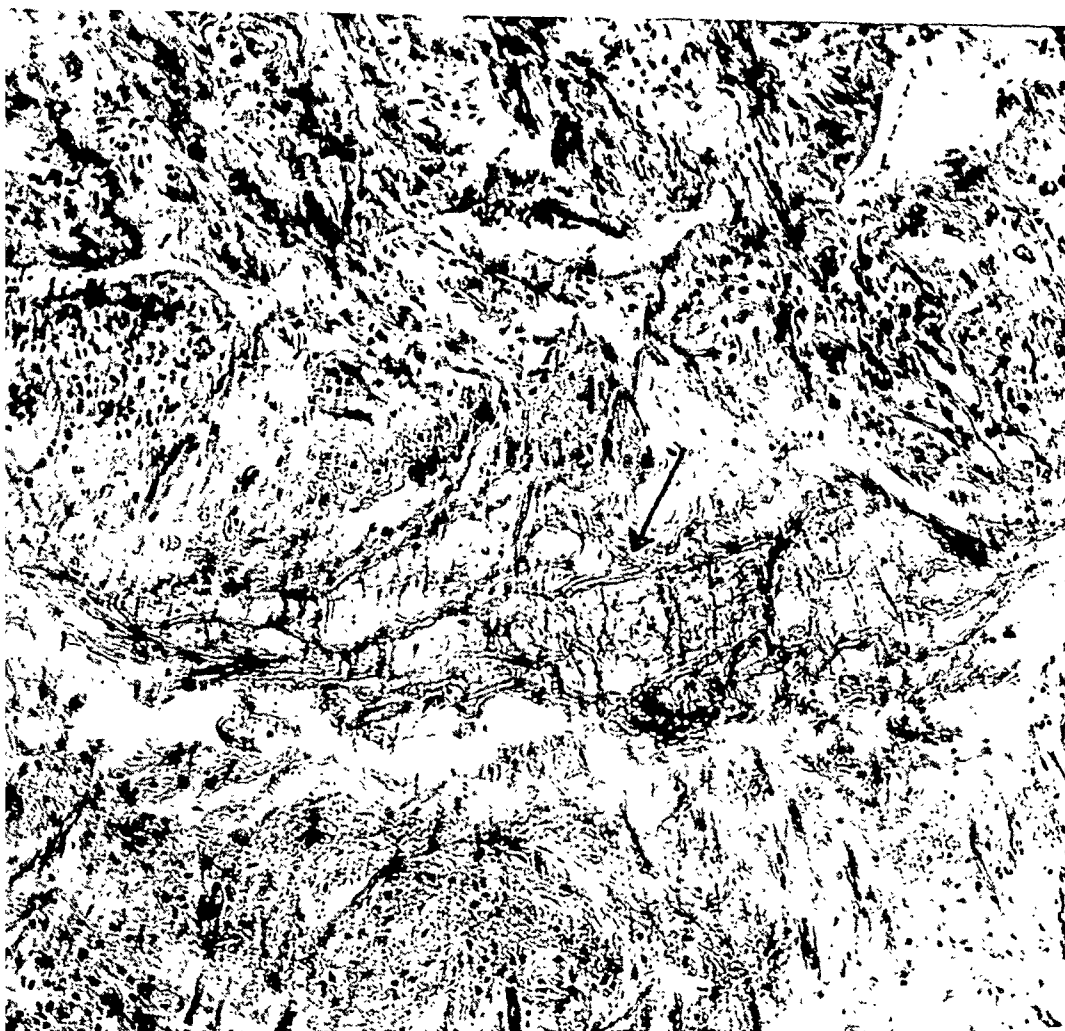


Fig. 1.—Photomicrograph of the axial portion of a completely obliterated appendix, showing the loosely anastomosing, large, nonmedullated nerve fibers (arrow). Masson's trichrome stain; $\times 213$.

central space with the muscularis mucosae closely apposed to it along the periphery in the manner of a capsule (fig. 3). The neuroma rarely breaks through this muscularis mucosae and extends into the submucosa. The number of neuromas may vary from one to many. When multiple, they are linked together by many nerve fiber strands, which stretch across from tumor to tumor like telephone wires. These neuromas contain a variable admixture of either argentaffin cells or lymphocytes.

Masson considers these neuromas infiltrated with lymphocytes to be undergoing retrogression. In the nonobliterated, still patent appendix, these neuromas can be easily found in the mucosa by the use of Mallory's phosphotungstic acid-hematoxylin stain and positively identified by Masson's trichrome stain. When treated with silver stains, it is observed



Fig. 2.—Photomicrograph of the axial portion of a completely obliterated appendix to show the still persistent muscularis mucosae (arrows) surrounding a few neuromas. Note the strands of nerve fibers running from one tumor nodule to another. Masson's trichrome stain; $\times 133$.

that the nonmedullated fibers are supported by a lacy network of very fine reticulum, having an intricate honeycombed appearance (fig. 4).

Incidence.—Among the 344 appendixes examined microscopically, there were 195, or 56.7 per cent, in which axial neuromas were found. Other rare and interesting findings were minute calcified bodies in the serosa and tuberculosis of the mucosa in 1 case each. One hundred

and sixty-five, or 48 per cent of all the appendixes, had a partially or completely obliterated lumen. Of the 195 cases of neuroma, 135, or 69.2 per cent, occurred in obliterated appendixes, and 60, or 30.8 per cent, in nonobliterated ones. The incidence of neuroma for all obliterated appendixes would then be 82 per cent, which figure closely agrees with Masson's 86 per cent.

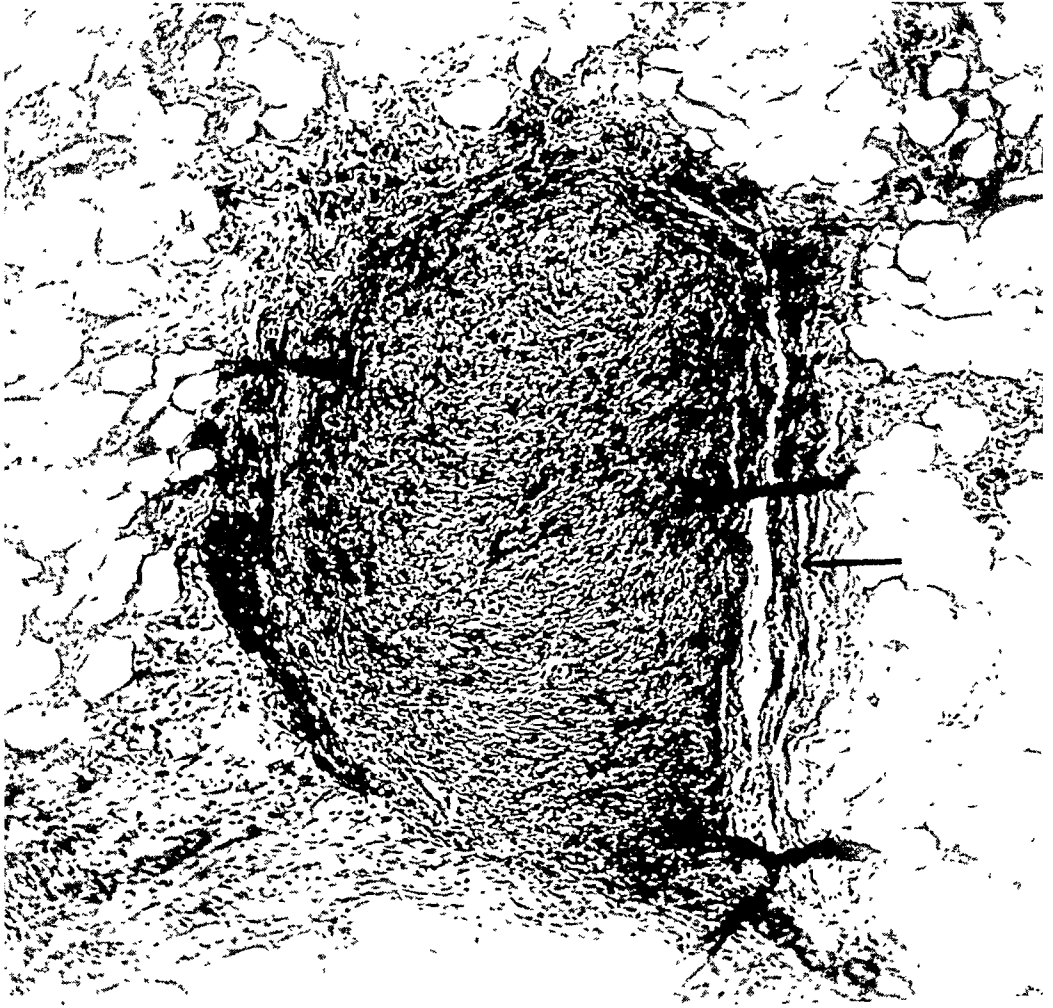


Fig. 3.—Photomicrograph of a well developed neuroma completely surrounded by the still persistent muscularis mucosae, simulating a capsule (arrow). Note the compact interlacing strands of nerve fibers. Masson's trichrome stain, $\times 133$.

The following short summaries of 6 representative cases are appended to show that neuromatosis of the appendix may simulate acute appendicitis, acute exacerbation of chronic appendicitis or chronic appendicitis. In neuromatosis, in spite of the apparent acuteness of the symptoms, the temperature and white blood count tend to remain within normal limits. Physical examination may even reveal a rigid abdomen, especially in the right lower quadrant, plus marked tenderness. In some cases, a rebound tenderness was present, and a test of the psoas

muscle was positive. The patient's agony may be so extreme that he literally doubles up or rolls about, trying to obtain relief; or his complaint may be merely of a dull ache or discomfort in the right lower quadrant with only a slight tenderness at McBurney's point. Nausea, with or without vomiting, ranged from mild to severe, and the attacks varied in number from one to many.

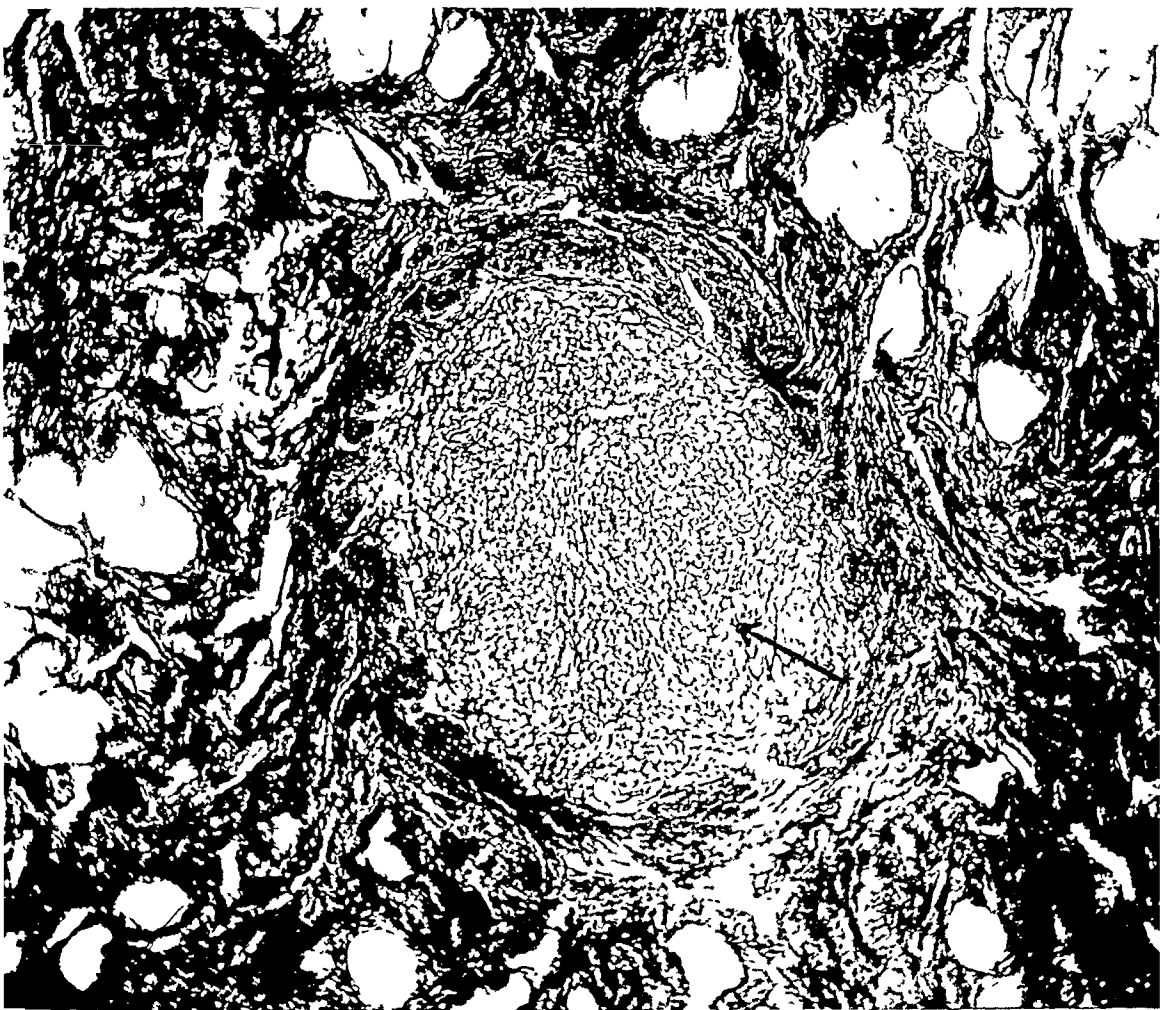


Fig. 4.—Photomicrograph of a neuroma to show the intricate lacy network of reticulum (arrow) forming a supportive tissue for the nerve fibers. Laidlaw's silver stain; $\times 134$.

REPORT OF REPRESENTATIVE CASES OF APPENDICULAR NEUROMATOSIS

CASE 1.—A man, aged 28, the day previous to admission was taken with severe pain around the umbilicus which radiated to the right lower quadrant. He described it as a feeling as though something was pulling on his navel from the inside. He was extremely nauseated and had to lie down. There were considerable pain and distress all night. On the morning of admission, the pain was localized in the right lower quadrant.

When the patient was 19 years old, he had a similar attack, which subsided in a few days under treatment by a physician. Over six months prior to admission, he had another colicky attack.

Physical examination showed marked tenderness in the right lower quadrant, both on pressure and on the rebound. Some tenderness was also elicited in the right flank. There was definite muscular spasm in the right lower quadrant. No palpable mass was felt in the abdomen. Rectal examination revealed tenderness on the right side. Urinalysis gave negative results. The white blood count was 5,900; a differential count gave 68 per cent polymorphonuclear leukocytes and 32 per cent lymphocytes. The temperature, pulse and respiration were normal. The patient was operated on for acute appendicitis, but only an obliterated appendix was found. No other pathologic process was found in the abdominal cavity.

CASE 2.—A woman, aged 31, prior to admission was seized with a dull cramping pain in the right lower part of the abdomen, which lasted about three days. She was nauseated but did not vomit. After that she had two similar attacks. Four days before admission, the fourth and most severe attack occurred, with much nausea but no vomiting. She had to stay in bed. Physical examination showed definite tenderness over McBurney's point and moderate spasm of the right rectus muscle. There was tenderness in the right vault on bimanual examination. The temperature, pulse and respiration were normal. Urinalysis gave negative results. The appendix removed at operation was of the obliterated variety; there was no pathologic condition of the pelvis. Figure 4 shows the microscopic changes.

CASE 3.—A woman, aged 37, following an attack of grip, experienced severe abdominal pains. At first, the pain was low in the right lower quadrant just above the inguinal ligament; later, it was slightly higher. She was in bed for seven weeks and had experienced some pain ever since. Examination showed tenderness in both lower quadrants, most marked on the right, with a good deal of rigidity of the right lower quadrant. Urinalysis gave negative results. The temperature was 98 F.; the pulse rate, 95, and the respiratory rate, 20. The appendix was found to be completely obliterated, without adhesions.

CASE 4.—A woman, aged 27, five days before admission began to have pain in the right lower quadrant, which was dull and constant, never sharp and severe. She did not sleep well that evening. The dull pain continued for the next two days. There was no nausea, vomiting, diarrhea, dysuria, chills or fever. The pain disappeared the day before admission and had not recurred. In the past, there was occasional indigestion with pains in the lower part of the abdomen, not at all severe. On physical examination, only a slight tenderness in the right lower quadrant was present. Urinalysis gave negative results. The temperature, pulse and respiration were normal. The appendix was found to be completely obliterated but nonadherent.

CASE 5.—A girl, aged 18, for the past three weeks had considerable pain in the right side. The pain started in the right side, and lasted for a day or so. It then went to the epigastric region and later returned to the right side. There had been no vomiting until two days prior to admission, when the patient became nauseated and vomited. Her bowels had been regular. During the last day or so, the pain had been worse. Examination showed tenderness and spasm over McBurney's point. The temperature was normal. Urinalysis gave negative results. At operation, the appendix was nonadherent and its lumen patent.

CASE 6.—A woman, aged 25, entered the hospital with the chief complaint of severe cramplike abdominal pain, more pronounced in the right lower quadrant. The pain came on suddenly and became progressively worse until admission. She

vomited only once. For the past three days she had a general digestive upset and became constipated. She had a similar attack two months prior to admission. On physical examination, there was great tenderness in the lower part of the abdomen, more marked in the right iliac region. The temperature was 98 F.; the pulse rate, 100, and the respiratory rate, 23. Urinalysis gave negative results. At operation, the appendix was grossly normal in size and shape, but was completely obliterated and bound down by adhesions. The gallbladder, stomach, fallopian tubes and ovaries were normal.

SUMMARY

Of 344 vermiform appendixes removed consecutively at operation and showing no evidence of acute inflammation, 165, or 48 per cent, had a distally or totally obliterated lumen and 195, or 56.7 per cent, showed neuromatosis.

Of the 195 cases of neuromatous growths, 135, or 69.2 per cent, occurred in obliterated appendixes and 60 cases, or 30.8 per cent, in nonobliterated ones. This gave an incidence of 82 per cent of neuromatous appendixes for all obliterated appendixes.

There was nothing characteristic grossly to indicate the presence of appendical neuromatoses. When the neuromatous growth was grossly noticeable, its cut surface appeared opaquely grayish white, usually without well demarcated borders. The larger growths in this series measured not more than from 1.5 to 2 mm. in diameter.

The number of neuromatous growths varied from one to many. When multiple, they were linked together by many nerve fiber strands. They appeared as loosely anastomosing strands of nonmedullated nerve fibers or as islands of compact interlacing bundles of spindle-shaped cells, always located central to the muscularis mucosae. If the neuromatous tumor mass was large enough, the muscularis mucosae was closely apposed to it along the periphery in the manner of a capsule. Rarely the tumor mass broke through the muscularis mucosae. These neuromatous growths contained a variable admixture of either argenta cells or lymphocytes.

The Masson trichrome stain should be employed before an appendix is discarded as being negative for neuromatosis.

LYMPHOCYTES IN THE PERIPHERAL BLOOD OF RABBITS FOLLOWING INJECTION OF FOREIGN SUBSTANCES

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PHILADELPHIA

The experiments reported in this paper are continuations of experiments previously reported by one of us,¹ in which the leukopenia and following leukocytosis induced by injections of sodium nucleinate and of vaccine were studied chiefly with regard to the total white cell count and the granulocytes. In the course of these experiments certain casual observations were made on the disappearance from the peripheral blood stream of the nongranular white cells and on their rate of reappearance. The data of these former experiments have been analyzed anew from the point of view of gaining information on the nongranular cells rather than on the granulocytes, and a number of new experiments have been carried out solely with this point in mind.

Ever since Arneth's² study of the effect of intravenous injections of various substances that cause a shift of the granulocytes to the left, an overwhelming amount of evidence has established some of the fundamental facts about the response of the granulocytes to foreign substances. To any one accustomed to injecting foreign substances intravenously into rabbits it is a commonplace observation that almost any kind of substance, especially proteins but also certain nonproteins, will cause an immediate peripheral leukopenia owing to redistribution of the white cells between the periphery and the deep viscera, which is followed in a few hours by a leukocytosis in which young forms of granulocytes are obviously numerous and which, therefore, represents increased delivery of new cells from the bone marrow.

In comparison to what is known about the granulocytes, little is known about the lymphocytes in regard to such matters as the possible

From the Department of Pathology, University of Pennsylvania Medical School.

1. Zeckwer, I. T.: *Arch. Path.* 7:1012, 1929.

2. Arneth, J.: *Die qualitative Blutlehre*, Leipzig, Dr. Werner Klinkhardt, 1920.

redistribution of cells within the vascular system, the conditions under which temporary peripheral lymphopenia may occur, the rate of the return of the lymphocytes to the previous level after temporary disappearance from the periphery, and the rate at which an absolute increase in the number of lymphocytes of the blood may be induced. Furthermore, attempts to recognize young forms of lymphocytes and to establish a "shift to the left" for the lymphocytes merit further study. The experiments reported in this paper were carried out in an attempt to elucidate some of these points.

EXPERIMENTAL PROCEDURE

Rabbits were used. For the leukocyte counts they were bled from a small incision in the marginal vein of the ear, care being taken to secure freely flowing blood. Every attempt was made to keep the animals free from excitement and vasomotor changes and to maintain their normal posture. A number of counts and smears were made before the foreign substances (suspensions of killed *Bacillus coli* or sodium nucleinate) were injected. Twenty-four hour cultures of *B. coli* on agar, suspended in salt solution, were killed, some in a water bath at 60 C. and others by autoclave. Sodium nucleinate was used in many experiments because, being nonprotein, it could be injected repeatedly without our having to consider the development of sensitization or immunization and because it was even more effective than foreign proteins in producing the phenomenon to be studied. Most of the sodium nucleinate used was dissolved in distilled water and brought just to the boiling point in order to sterilize it. One batch was autoclaved and therefore may represent disintegration products of sodium nucleinate. In a few experiments nucleic acid was dissolved in weak sodium hydroxide. The agent used is indicated in the table.

Blood films were stained by Wright's method or by superimposing Giemsa's stain on an unwashed Wright stain (Wiseman³). Following the intravenous injections, films and total white cell counts were made at varying intervals and the percentage values of cells translated into absolute values. In the films stained by the special stain, the lymphocytes were classified as to age on the basis of the degree of basophilia, according to the criteria of Wiseman. In the table, lymphocytes and monocytes are grouped together as nongranular cells.

In nine rabbits, splenectomy was carried out under aseptic conditions. A number of days later, the cellular response to the injections was studied.

RESULTS

Experiments 1 to 8 were the experiments in which the data on granulocyte counts were published but in which the data on lymphocytes were not described.¹ Experiments 9 to 18, the data on which have not previously been published, were experiments carried out with the sole purpose of studying the nongranular cells.

Involvement of Nongranular Cells as Well as of Granulocytes in the Peripheral Leukopenia Following Injections.—In every experiment,

3. Wiseman, B. K.: J. Exper. Med. 54:271, 1931.

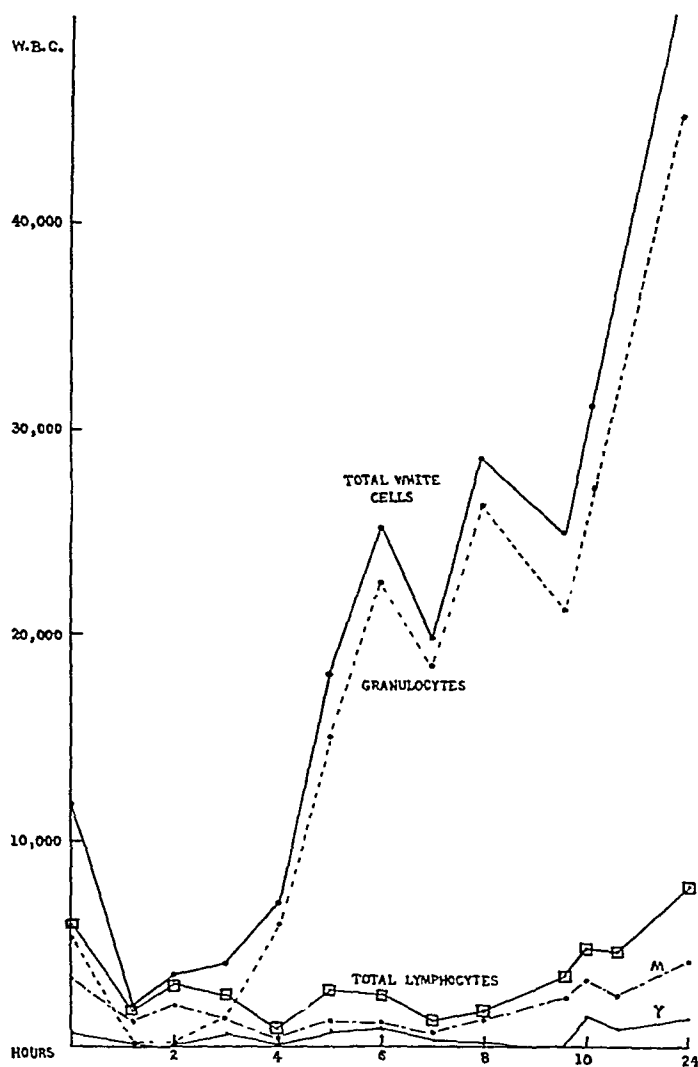
Data on Eighteen Experiments

Ex- peri- ment	Rab- bit	Date	Experimental Condition	Injec- tion	Gm. In- jected	Time in Hours When Nongranular Cells Rose from Lymphopenic Level	Time in Hours When Granulo- cytes Rose from Leukopenic Level
I. Effects of Injection of Suspensions of B. Coli							
1	1	9/13/28	Animal intact	1st*	Not within 4½	Before 4½
		9/19/28	5 days after splenec- tomy; white blood cells, 16,000	2d*	Not within 6	Before 3
		9/26/28	12 days after splenec- tomy; white blood cells, 22,800 (in- fected leg)	3d*	Not within 6	Before 3½
2	3	9/17/28	Animal intact	1st*	Not within 6½	Before 4½
		9/24/28	4 days after splenec- tomy	2d	Not within 3	Before 2
3	5	10/16/28	11 days after splenec- tomy	1st	Before 20	Before 20
		10/19/28	14 days after splenec- tomy	2d	Not within 3	Before 3½
II. Effects of Injection of Sodium Nucleinate							
4	8	10/29/28	Animal intact	1st	0.15	Before 24	Before 24
		10/31/28	Animal intact	2d	0.10	Before 24	Before 24
		11/ 1/28	Animal intact	3d	0.05	Before 24	Before 24
		11/ 8/28	Animal intact	6th	0.10	Before 23	Before 23
5	10	11/20/28	14 days after splenec- tomy; white blood cells, 27,000 (in- fected leg)	2d	0.10	Before 3	Before 2½
6	11	11/27/28	Animal intact	1st	0.50	Before 7	Before 7
		12/ 5/28	Animal intact	2d	0.50	Before 5½	Before 5½
		12/11/28	5 days after splenec- tomy	3d	0.50	Before 3½	Before 3½
7	12	11/26/28	Animal intact	1st	0.10	Not within 5½	Before 5½
		12/ 3/28	Animal intact	2d	0.10	Not within 6	Before 5
8	13	12/ 4/28	Animal intact	1st	0.10	Between 3½ and 4	Between 3½ and 4
		12/12/28	Animal intact	2d	0.10	Before 7	Before 7
9	93	2/26/32	Animal intact	1st	0.20	Before 20	Before 20
10	A	4/ 3/32	Animal intact	1st	0.20*	Not within 4	Before 3
		4/12/32	Animal intact	2d	0.20*	At 4	At 4
		6/17/32	Animal intact	3d	0.20	Before 12	Before 12
11	B	4/17/32	Animal intact	2d	0.20*	Not within 3	Before 2
				3d	0.20*	Before 15	Before 15
				4th	0.20*	Before 25	Before 25
12	C	4/ 7/32	Animal intact	1st	0.20*	Not within 5	Before 4
		4/13/32	Animal intact	2d	0.20	Before 15	Before 15
		6/16/32	10 days after splenec- tomy	2d	0.20	Before 16	Before 15
13	D	4/14/32	Animal intact	1st	0.20	Before 21	Before 21
		6/23/32	17 days after splenec- tomy	2d	0.20	Before 20	Before 20
14	E	4/11/32	Animal intact	1st	0.20	At 5	At 4
		6/23/32	28 days after splenec- tomy	2d	0.20	At 7	At 4
15	F	4/12/32	Animal intact	1st	0.20*	Before 3	Before 3
		6/17/32	Animal intact	2d	0.20	Before 17	Before 17
16	94	6/16/32	Animal intact	1st	0.60*	Before 25	Before 25
17	G	6/ 8/32	1 month after sple- nectomy	1st	0.20	Before 5½	Before 4
18	100	1/13/33	Animal intact	1st	0.20	At 9	At 4

* Autoclaved.

the absolute number of nongranular cells dropped as rapidly as that of the granulocytes (chart).

Although we did not make lymphocyte counts on blood from the viscera, it is reasonable to assume that the rapid disappearance of these cells from the peripheral circulation means accumulation in the deep viscera. The simultaneous disappearance of nongranular cells and



Response of intact rabbit 100 (experiment 18) to the first injection of sodium nucleinate; *M* signifies lymphocytes of medium age; *Y*, young lymphocytes.

granulocytes from the periphery lends support to the theory that vaso-motor changes may be a factor in the redistribution of leukocytes, a point that will be discussed later.

Time of Increase of Nongranular Cells in the Peripheral Circulation in Relation to That of Granulocytes.—It will be seen from the table that the return increase of nongranular cells after the leukopenic period was in a few experiments almost coincident with the increase of the

granulocytes (experiments 6, 8, 10, 15 and 17), but that in most experiments the nongranular cells lagged behind the granulocytes, as is shown in the chart. When the granulocyte count was high, owing to infection or a previous injection, the granulocytes responded especially rapidly (experiments 1 and 5). Consideration was given to the well established fact that the number of leukocytes fluctuates enormously from time to time under physiologic conditions. Therefore fluctuations were not considered significant unless the levels reached differed greatly from the preinjection ones, and were well beyond the limits for normal given by Pearce and Casey⁴ and others for the rabbit.

Whitney⁵ recently reviewed some of the literature on lymphocytosis. Doan and his co-workers⁶ "never observed a subsequent lymphocytosis of any moment" after injections of sodium nucleinate, and recently Doan⁷ reported that after often-repeated injections of nucleinate a relative and absolute lymphopenia occurs. Among recent studies on the production of lymphocytosis, Wiseman gave data on lymphocytes in rabbits with active tuberculous infection⁸ and after repeated injections of protein,⁸ and Ehrich⁹ gave data on lymphocytes after subcutaneous infection of rabbits with staphylococci and after repeated intravenous injections of killed staphylococci. Most of the work mentioned dealt with repeated injections or with infections in which the organism was continuously alive. In our experiments we were dealing with the effect of a single injection and with the effect of several subsequent injections. In 5 rabbits we found a slight increase in lymphocytes, roughly up to double the original values, about twenty-four hours after injection.

Types of Lymphocytes in the Peripheral Blood Under the Given Experimental Conditions.—When the lymphocyte count begins to rise after the lymphopenia, the question arises whether the increase represents a return to the general circulation of the lymphocytes formerly present that have been stored in the deep viscera (a reestablishment of equilibrium), or whether it represents the entrance of new lymphocytes into the blood from their sites of origin, or a mixture of both processes. When the number of granulocytes rises, it is known from the morphology of the cells that the marrow has been actively stimulated by the injection to discharge young cells into the blood stream. One commonly thinks of lymphocytes as being delivered into the blood stream much less readily than granulocytes. It is known that granulocytes

4. Pearce, L., and Casey, A. F.: J. Exper. Med. **52**:39 and 167, 1930.

5. Whitney, C.: Medicine **7**:1, 1928.

6. Doan, C. A.; Zervas, L. G.; Warren, S., and Ames, O.: J. Exper. Med. **47**:403, 1928.

7. Doan, C. A.: Proc. Soc. Exper. Biol. & Med. **29**:1030, 1932.

8. Wiseman, B. K.: J. Exper. Med. **53**:499, 1931.

9. Ehrich, W.: J. Exper. Med. **49**:347 and 361, 1929.

pass directly into the venous blood stream, whereas many lymphocytes from their point of origin in the lymphoid tissue to their indirect entrance into the blood stream pass through the more slowly moving fluid of lymphatic ducts. From the experiments of Lee¹⁰ on the cat, the indication is that roughly one half of the circulating lymphocytes reach the blood stream through the thoracic duct. From data given by Rous,¹¹ Bunting and Huston¹² calculated that the rate at which lymphocytes are delivered from the thoracic duct into the blood stream is 3,300,000,000 in twenty-four hours, and that after excluding entrance of lymphocytes from the spleen and the thoracic duct in the rabbit, 443,000,000 lymphocytes disappeared from the circulation in six hours. However, Ehrlich⁹ recently demonstrated that in hyperplastic lymph nodes resulting from staphylococcic infection in rabbits enormous numbers of lymphocytes may pass directly into the veins at the time of the greatest lymphocytosis in the peripheral blood; and it is well established that with contraction of the spleen under sympathetic stimulation or after the administration of epinephrine lymphocytes are squeezed from the pulp into the circulation in sufficient numbers to raise considerably the lymphocyte count in the peripheral blood. There is even evidence that the smooth muscle of lymph nodes contracts and causes lymphocytosis (Martin¹³).

One commonly thinks of lymphocytes as reacting to foreign substances much more slowly than granulocytes. Their locomotion is slower, and they are not phagocytic cells. The granulocytes respond rapidly in acute infections, while the lymphocytes are prominent only in the later stages of inflammation. It would, therefore, seem that in some of the experiments in which the number of lymphocytes rose so rapidly after the leukopenic period the increase was due not to any property of the cells but to the attendant physiologic factors, such as vasomotor changes, which may be responsible for these shifts.

Wiseman's³ studies offer a possible means of determining whether the lymphocytes which appear after the leukopenic period are new or old cells. He concluded that the degree of basophilia, as observed with the staining method used by him, is a good index of the age of the cells. He divided the lymphocytes into: (1) the Y type, young lymphocytes, either small or large, the cytoplasm of which stains with the intense blue coloring of a blue glass marking pencil; (2) the M type, cells of medium age, either small or large, the cytoplasm of which stains sky blue, and (3) the O type, the oldest cells, again either small or large, the cytoplasm of which stains so faintly that it is almost colorless.

10. Lee, F. C.: *J. Exper. Med.* **36**:247, 1922.

11. Rous, F. P.: *J. Exper. Med.* **10**:238 and 329, 1908.

12. Bunting, C. H., and Huston, J.: *J. Exper. Med.* **33**:593, 1921.

13. Martin, H. E.: *J. Physiol.* **75**:113, 1932.

Under normal conditions, very few young forms appear in the circulation, and cells of medium age are slightly more numerous than the old ones. In our experiments in which this classification of lymphocytes was made (experiments 11 to 18), the fluctuations involved chiefly the M type. There is naturally considerable personal equation in classifying cells in this manner, there being marked discrepancies between records made by different persons. However, as the Y cells are the most distinctive, a significant increase in Y forms would have been the easiest to detect. Sometimes the Y forms showed a slight increase, but the fluctuations in the total lymphocyte count depended on fluctuations in the M forms (chart), and in no instance did the Y forms increase to the extent of raising significantly the preinjection level. If we grant Wiseman's conclusions that the basophilia of the cytoplasm is a good criterion of age, the results would indicate that the return rise of lymphocytes, after the lymphophenic period, is largely a rise in mature forms of medium age, which probably represents a return to the circulation of the cells which had been in circulation or reserve before the injection, and that the injected substance exerts only a slight stimulus to the discharge of new young lymphocytes. This, of course, differs from the rise in granulocytes, during which young cells are conspicuous. However, if we accept the hypothesis that the M lymphocytes not only circulate but are held in reserve in lymph tissue storage centers, their increase, taken with the slight increase of young forms, would indicate that additional cells are released; i. e., there is a process similar to that of the granulocytes.

Effect of Splenectomy.—In intact animals various fluctuations were observed during the leukopenic period, which were thought probably to represent a discharge of white cells into the circulation by the contraction of the spleen under sympathetic stimulation. A number of splenectomized rabbits were studied to see whether these fluctuations were eliminated. Furthermore, since it is possible that many new lymphocytes may pass directly from the spleen to the blood stream, it was determined to see whether removing the spleen altered significantly the lymphocyte counts following injection. The results indicated that removal of the spleen did not appreciably alter the cellular response to the injections.

COMMENT

The immediate disappearance of granulocytes from a vein of the ear after intravenous injections is known to be a redistribution of cells from the periphery to the deep organs; but how this redistribution occurs is difficult to explain. One possibility is that the foreign substance is rapidly taken up by the reticulo-endothelial system and that the granulocytes accumulate in the same areas in the process of phago-

cytosing the particles. Yet the same phenomenon of redistribution occurs when the substance is not particulate matter; and the lymphocytes also, even though they do not function in phagocytosis, disappeared from the periphery in our experiments. The latter fact and the rapidity of the occurrence of the phenomenon suggest the possibility of a vasomotor change being a factor.

Camp¹⁴ found that in rabbits the subcutaneous injection of drugs which produce an increase in tone of the sympathetic nervous system caused a decrease in the percentage of lymphocytes and an increase in the percentage of neutrophils, while drugs which produce an increase in parasympathetic tone caused a decrease in the percentage of neutrophils and an increase in the percentage of lymphocytes. Total leukocyte counts and absolute values for neutrophils and lymphocytes are not given in his paper, so it is impossible to know exactly what the changes in the blood were if the total count was changing, which is likely. The author concluded that "the distribution of leukocytes in the peripheral circulating blood of rabbits is controlled by the autonomic nervous system. The partition of leukocytes in the peripheral circulating blood is an index of autonomic balance, the lymphocytes running parallel to parasympathetic tone, and the neutrophils to sympathetic tone." It is conceivable that changes in vasomotor tone result in shifts of blood cells within the vascular system, but it is difficult to see how such changes in tone could have any selective effect on neutrophils or lymphocytes, except so far as contraction of the spleen or lymphoid tissue under sympathetic stimulation results in squeezing lymphocytes out of the pulp into the general circulation; Camp's results, however, appear to be in the opposite direction as far as can be determined without knowing the absolute values. Bueno¹⁵ also ascribed fluctuations in the leukocyte count to changes in the balance between the sympathetic and the parasympathetic system. Sabin, Cunningham, Doan and Kindwall¹⁶ discussed some of the older literature on the effect of the vasomotor state on leukocytes.

Mueller, Petersen and Hölscher¹⁷ stated that intravenous injections of bacteria cause peripheral vasoconstriction and peripheral leukopenia, with simultaneous splanchnic dilatation and leukocytosis in the liver, spleen and gastro-intestinal tract. Mueller¹⁸ expressed the belief that with intracutaneous injections also peripheral leukopenia is a vasomotor

14. Camp, W. J. R.: *J. Lab. & Clin. Med.* **13**:206, 1927.

15. Bueno, A. L. P.: *Brazil-med.* **2**:266, 1925; abstr., *J. A. M. A.* **86**:519, 1926.

16. Sabin, F. R.; Cunningham, R. S.; Doan, C. A., and Kindwall, J. A.: *Bull. Johns Hopkins Hosp.* **37**:14, 1925.

17. Mueller, E. F.; Petersen, W. F., and Hölscher, R.: *Proc. Soc. Exper. Biol. & Med.* **27**:544, 1930.

18. Mueller, E. F.: *Arch. Int. Med.* **37**:268, 1926.

phenomenon. He maintained that this leukopenia usually affects only the granulocytes and not the lymphocytes. Again it seems difficult to conceive of a vasomotor change which could affect only one kind of white cell and not the other unless physical properties, such as adhesiveness, retain the granulocyte in the visceral blood vessels. Garrey and Butler¹⁹ considered that fluctuations in leukocytes depending on exercise are "attributable to circulatory shifts with the liberation of leukocytes trapped in unused capillaries." Butler and Garrey²⁰ found that in a sympathectomized dog neither exercise, carbon dioxide nor heat caused fluctuations in leukocytes. It would be interesting to know how such an animal would respond to intravenous injections of agents ordinarily producing leukopenia.

Beard and Beard²¹ found that when sodium chloride was injected intravenously leukopenia resulted, in which the fall in polymorphonuclears was striking, while the lymphocyte count sloped downward more gradually. A rapid return rise of polymorphonuclears occurred, but the lymphocytes continued to drop during the period of observation (up to three and one half hours). Elvidge²² found that after the intravenous injection of quartz into rabbits "both polymorphs and lymphocytes take part in the leukocytosis as well as the leukopenia; the polymorphs are usually, though not always, the first to increase in number, being closely followed by the lymphocytes." After the injection of india ink, however, "the lymphocytes are the first to respond." Andrewes²³ found that after the intravenous injection of various living and dead bacteria the lymphocytes fell as well as the polymorphonuclears but not so rapidly, and that the lymphocytes might be much slower than the polymorphonuclears in rising but might eventually pass their normal limits. Wells²⁴ stated that after the intravenous injection of different bacteria, the lymphocytes showed no definite change during the period of polymorphonuclear fall and rise.

Doan⁷ and his co-workers, after studying the effect of injections of sodium nucleinate, stated that the lymphocytes "may or may not decrease in absolute numbers during the leukopenia period." Fox and Lynch²⁵ in earlier experiments with dogs found that the lymphocytes as well as the granulocytes dropped after the administration of nucleic acid and of sodium nucleinate. In our experiments we invariably found that after the injection of various foreign substances a decrease in the

19. Garrey, W. S., and Butler, W. E.: *Am. J. Physiol.* **90**:355, 1929.

20. Butler, V., and Garrey, W. S.: *Am. J. Physiol.* **98**:394, 1931.

21. Beard, L. A., and Beard, J. W.: *Am. J. Physiol.* **85**:169, 1928.

22. Elvidge, A. R.: *J. Path. & Bact.* **31**:33, 1928.

23. Andrewes, F. W.: *Lancet* **2**:9, 1910.

24. Wells, C. W.: *J. Infect. Dis.* **20**:219, 1917.

25. Fox, H., and Lynch, F. S.: *Am. J. M. Sc.* **153**:571, 1919.

lymphocytes occurred in the peripheral blood coincident with the fall in granulocytes. If this is true, a vasomotor change must be considered as a possible factor in redistributing the cells. The fall in blood pressure noted¹ is evidence of circulatory changes.

If a vasomotor change is responsible for shifting cells from one region to another, or for changing the ratio of cells to plasma, the red cells should be simultaneously affected, and to test this point, red blood cell counts were carried out in two rabbits before and shortly after the injection of sodium nucleinate. The red cells showed some fluctuations but none commensurate with the fluctuations in the leukocytes; so it seems likely that any vasomotor changes which occur are associated phenomena and bear no causal relation to the cellular distribution. In their experiments with sodium chloride Beard and Beard found no marked fluctuations in the red cells.

Although no definite conclusions can be drawn from the experiments reported in the literature or from our own experiments, it can be tentatively suggested that any vasomotor changes are accompaniments rather than the cause of the redistribution of leukocytes after intravenous injections.

SUMMARY

Following the intravenous injection of various foreign substances into rabbits there was an immediate decrease in the number of non-granular white cells as well as in the number of granulocytes in the peripheral blood.

Following the leukopenic period, the return rise of nongranular cells in our experiments was usually subsequent to the rise of granulocytes, and occasionally simultaneous with it.

The criteria advocated by Wiseman for gaging the maturity of lymphocytes were applied to see if they would indicate whether the lymphocytes appearing after the leukopenic period were new or old cells. Although the Y cells sometimes showed a slight increase, the fluctuations in the total lymphocyte count were dependent on the number of M cells, which probably represented a return of cells to the general circulation from temporary depots. The possibility of the entrance of reserve cells of medium age (i. e., a process similar to that of the granulocytes) is also discussed.

In these experiments splenectomy did not alter significantly the lymphocytic response.

Laboratory Methods and Technical Notes

NEW SIMPLE QUANTITATIVE MICROCRYSTALLOGRAPHIC ESTIMATION OF PHOSPHATES IN BLOOD SERUM

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A microcrystallographic method for the estimation of phosphates in the urine has been described in a previous article.¹ The method consists in precipitating the phosphates with an ammonium magnesium sulphate reagent (Dowd's reagent), calculating the quantity of phosphates from the type of crystals of magnesium ammonium phosphate. The attempt to apply this method to the estimation of phosphates in the blood serum did not succeed, as the crystal type formed by precipitating the serum phosphates is the lowest one (type 8 of figure 1 in the previous paper); in other words, the quantity is less than 10 mg. per hundred cubic centimeters of blood. Further dilutions do not change the type of the crystals, but make them disappear. The disappearance of the crystals has been used for a quantitative method. Certain technical conditions had to be considered, however, in making the proper dilutions. A dilution with water or with a saline solution isosmotic to the blood would change the optimum conditions for the formation of the crystals, which, as stated in the previous article, corresponds to the specific gravity of the urine. In order to secure the optimum salt concentrations the dilutions of the serum were made with a 2.5 per cent solution of sodium chloride. Furthermore, the formation of the crystals depends on the time factor. Forty-five minutes has been found empirically to be necessary for the formation of crystals in a 2.5 per cent solution of sodium chloride containing 3 mg. of phosphorus as phosphoric acid (or its salts) in 100 cc. of the fluid. Further dilutions of this fluid do not precipitate within this time.

Therefore the highest dilution of a serum made with a 2.5 per cent solution of sodium chloride which will give a type 8 crystal within forty-five minutes contains 3 mg. of phosphorus per hundred cubic centimeters of blood serum. This consideration gave the fundament for the microcrystallographic titration of the phosphate in the serum.

METHOD

The requirements are: 0.6 cc. of the unknown blood serum; two capillary pipets holding 0.1 cc. each, graduated into 0.01 cc.; eighteen test tubes, 3 by $\frac{3}{8}$ inches (7.6 by 0.95 cm.); Dowd's² reagent: magnesium sulphate, 1 ounce (28.4 Gm.); ammonium sulphate, 1 ounce (28.4 Gm.); ammonium hydroxide, 10 per cent, 1

1. Pribram, E. .: Arch. Path. **15**:213, 1933.

2. Dowd, J. H.: Illinois M. J. **56**:286, 1924.

fluid ounce (30 cc.); distilled water, 8 fluid ounces (240 cc.), and a 2.5 per cent solution of sodium chloride.

Set up two rows of tubes with nine tubes in each row. In each tube of the front row place 0.06 cc. of serum; to the second tube of this row add 0.01 cc. of the 2.5 per cent solution of sodium chloride; to the third, 0.02 cc.; to the fourth, 0.03 cc., etc., increasing by 0.01 cc. the contents of each of the remaining tubes. Mix well and transfer exactly 0.05 cc. of the diluted serums to the corresponding tube in the second row. To this 0.05 cc. add 0.01 cc. of Dowd's solution and mix immediately. Let the mixture stand for forty-five minutes and examine it for crystals. The last tube containing crystals contains 3 mg. of phosphorus per hundred cubic centimeters. Determine the total amount of phosphorus in the serum by means of the following tabulation:

Last Tube Containing Crystals	Mg. of Phosphorus per 100 Cc.
9	7
8	6.5
7	6
6	5.5
5	5
4	4.5
3	4
2	3.5
1	3

Comparison of this method with the colorimetric method showed that the colorimetric method gave 4.2 mg. in 100 cc. of serum, and the microcrystallographic method, 4 mg. in 100 cc. of serum. The difference of 0.2 mg. per hundred cubic centimeters is caused by the difference in the two methods, as the intervals used in the dilutions of the microcrystallographic method do not allow the estimation of less than 0.5 mg. per hundred cubic centimeters. These differences, however, are within physiologic limits.

The practical application of the method will be described in further articles.

SUMMARY

The precipitation of phosphates by means of a proper ammonium magnesium sulphate reagent (Dowd's reagent) can be used for a quantitative estimation of the phosphates in the blood serum. Equal quantities of serum, diluted with increasing amounts of a 2.5 per cent solution of sodium chloride, are precipitated with the reagent; the last tube in which the crystals are found within forty-five minutes contains 3 mg. of phosphorus in 100 cc. of serum. The percentage of serum phosphates is calculated from the dilution.

General Review

HODGKIN'S DISEASE

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A century ago Thomas Hodgkin presented 7 cases of a peculiar lymphadenopathy with anemia, and so called attention to the obscure disease that bears his name. Despite the uncertainty as to the true nature of the disease, much has been accomplished in these years; this review is presented in order to sum up and to correlate as far as possible the accumulated literature. It has been compiled rather as a supplement to, or a continuation of, several outstanding reviews and monographs than as a complete survey of the subject.

NOMENCLATURE

Perhaps no other disease has been encumbered with a more surprising array of names than has Hodgkin's disease. Even special features, such as those of symptomatology, pathology and histology, are presented by the various writers under a terminology which seems to vary according to individual preference or invention. Such a state of affairs is deplorable and has made progress more difficult than it need be. In order to call attention to this situation, the following designations were extracted from the literature; direct translations into other languages of several of the more common names are not included:

Hodgkin's disease, Reed-Hodgkin's disease, Pel-Ebstein disease, Paltauf-Sternberg's disease, maladie de Hodgkin-Paltauf-Sternberg, Sternberg's disease, Hodgkin-Wilks' disease, multiple lymphoma, malignant lymphoma, Hodgkin's granulomatous lymphoma, lymphomatosis granulomatosa, chronic lymphomatosis, chronic malign lymphomatosis, chronic benign lymphomatosis, malignant infectious granuloma, Hodgkin's granuloma, granulomatosis, granulomatosis textus lymphaticæ, malignant granuloma, Sternberg's malignant granuloma, das chronische Rückfallsfieber, progressive lymph node hypertrophy, lymphogranuloma, lymphogranulome tuberculeux, malignant lymphogranuloma, lymphogranulomatosis spleno-meseraica, lymphogranulomatosis, eosinophilic lymphogranulomatosis, lymphogranulomatosis perniciosa, lymphogranuloma of the Hodgkin type, lymphogranulomatosis Paltauf-Sternberg, lymphadenoma, lymphadenome métatypique, adénie, adenomycosis, adénite prurigène éosinophile, anemia lymphatica, anemia splenica, pseudoleukemia, multiple lymphadenome ohne leukemia, infectious form of pseudo-leukemia, acute pseudo-leucocythaemia, cachexia sans leucémie, aleukemic malignant lymphoma,

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lymphoblastoma, lymphoblastoma of the Hodgkin type, scirrhus lymphoblastoma, lymphosarcoma of the Hodgkin type, desmoid carcinom, malignes Lympho-Sarcom, megakaryoblastoma.

I wish to enter a protest against certain tendencies in nomenclature which are apparently on the increase. Since the etiology, or even the exact status of the disease is not known, it can but add to the confusion if cases, and especially series of cases, are described under titles which may perhaps express the respective writers' individual ideas, but which have not been generally accepted. Valuable statistics are buried, often beyond reclaim, under the name "lymphoblastoma," which includes a whole list of pathologic conditions; the term "lymphogranuloma" is incorrect in many cases, for it does not include all of the possibilities, and other names have similar defects. It would seem to be preferable to retain the older name of "Hodgkin's disease," or possibly the widely recognized term of "lymphogranuloma," at least until the actual status and etiology of the condition are shown. The latter term is conveniently abbreviated to "Lg," especially by European authors.

INCIDENCE

Symmers, in a review of 8,485 general autopsies performed at Bellevue Hospital, New York, during fifteen years, collected 14 cases of lymphogranuloma, representing 0.16 per cent. Barron, reviewing 7,253 general autopsies, found 24 cases, 0.32 per cent. These two analyses combined give the following result: among 15,783 cases of disease in general there were 38 of lymphogranuloma, or 0.24 per cent. Pack and Le Fevre found records of 335 cases in the Memorial Hospital, New York, which represented 1.75 per cent of all admissions. As this hospital has a very extensive service for the treatment of patients with tumors, the incidence is higher than the average, which might be considered as considerably less than 1 per cent of all deaths.

Brandt (Latvia), Harbitz (Norway), DeJong and others believed the disease to be increasing. In the discussion of Aubertin and Destouche's paper, the consensus was that the disease has increased in frequency since the World War; Rist made the point that biopsies are now more generally used in diagnosis, and hence, the supposed increase. Fox believed essentially the same thing. Fox and Farley, in 1922, noted that diseases of the lymph nodes with enlargement and without an increase of leukocytes in the blood had become more frequent in recent years. Much, of course, is to be said for the general trend toward more accurate diagnosis by biopsy. It is astonishing, however, how frequently cases are reported with a diagnosis of lymphogranuloma in which no microscopic studies were made, in spite of the universal recognition of biopsy as a requisite for the diagnosis of this condition.

DURATION

This phase has been rather well covered by numerous authors. I hesitate to generalize as to the duration of the disease, believing that each case is affected by so many different factors that such statistical handling might tend to obscure rather than to clarify. Burnam mentioned treatment, hard work, poor food and intercurrent infections as important influencing factors. To these may be added the age at onset, the disease being more malignant in children than in adults (Ziegler, Borsutsky, Fabian), and also the fact, as stated by Terplan and Mittelbach, that in young adults the course is more apt to be chronic. Rolleston cited the case of Brunner's patient who died after but two weeks of symptoms suggesting cardiac failure, the autopsy revealing extensive lymphogranulomatosis; this case is thought-provoking when one considers others of apparently short duration, for the disease had possibly been under way for a much longer time. Other cases of short duration were reported by Weber and Bode (eleven weeks); Ziegler (one month) and Barron (two months). I observed a case in which the patient survived only seven weeks after the apparent onset.

The average duration from onset to death, according to various observers, is as follows (stated in months): Cunningham, thirty-six; Desjardins and Ford, thirty-one; Burnam, twenty-four; Longcope and McAlpin, twenty-four; Simmons and Benet, twenty-four; Vasiliu and Goia, thirty; Klewitz and Lullies, twenty; Blackford, thirty-six and six tenths; Barron, seventeen; Wellbrock and Loughery, thirty-one; Corbeille, twenty-two and five-tenths (children); Borsutsky, twenty-two (children); Acuña and Casaubón, twenty (children). The duration in the series of cases in children shows remarkable agreement.

MacNalty stated that the duration tends to be more prolonged in cases involving the superficial nodes than in those in which the internal nodes alone are involved. Blackford, in discussing Muller and Boles' paper, felt that cases might be divided into two classes as to duration and course: (1) those in which the patients died within two years and (2) those in which the patients, surviving this apparently critical period, lived more than six years. This dividing line he believed to be quite sharp. Cunningham stated: "The prognosis of longevity in Hodgkin's disease is an uncertain factor even when there is an extensive involvement." He estimated the average duration as three years but cited a case in which the patient lived twenty-five years.

Regarding the influence of treatment on duration, there is again a variety of opinion. It will be preferable to discuss this aspect under treatment.

After analysis of a large number of cases, the average duration is estimated at about twenty-four months, tending to be more than two years rather than less.

SEX

Several authors have given the ratio of male to female patients. The following figures represent a compilation from twenty-one publications, with mention of a total of 1,447 patients, 1,009 males, and 438 females. The ratio of males to females is 2.3:1. This ratio appears to be well established, and it is believed that it represents a rather true value, supplanting ratios based on a much smaller number of patients. The ratio is even more striking in children 15 years of age or less: total patients, 77; male, 64; female, 16; ratio of male to female, 4:1.

The significance of these figures cannot, of course, be settled at this time. That there is a definite preponderance of male patients is apparent. Bunting has already stated that "age and sex importantly influence the susceptibility of the lymphoid tissue to disease," and that they also play a part in the rate of progress of the disease process. Gemmell, in a study of 57 cases in females, came to some highly interesting and original conclusions. He believed that the female has more protection against the disease than has the male, and he indicated the ovary as the seat of such protection. He therefore concluded that "as long as there is sufficient ovarian hormone in the general circulation, the individual can resist the disease," and that "possibly Hodgkin's disease occurs, in the female, chiefly when there is a hypo-function of the ovary."

AGE

There are numerous figures in the literature regarding the ages of patients. Unfortunately, few writers state whether the age represents the time of onset, of the first consultation or of death. Such knowledge is, of course, indispensable in a statistical study. However, with the available data, the following facts seem reasonably well established. The disease occurs most frequently in young adults (from 18 to 38 years), but may occur in persons of any age. The youngest patient whose case is recorded was the child observed by Priesel and Winkelbauer, who was $4\frac{1}{2}$ months old at death and apparently was born with the disease. Wollstein and McLean reported a case of thymic Hodgkin's disease in a child $4\frac{1}{2}$ months, and Pinelli, a case in a child of 6 months.

Corbeille noted that more than half of the cases occurring in children begin during the first five years of life. After a study of the literature, as well as observation of personal cases, I feel that this is true. Furthermore, it is surprising how few of the cases occur at the period of puberty. Of 33 cases in children 15 years old or younger, only 2 occurred between the ages of 12 and 14. The drop in the curve is remarkable. I recognize, of course, that puberty occurs at different ages in different persons.

It is my opinion that both sex and age are definitely involved in this disease.

HISTOLOGY

The historical aspects are interesting. The earliest description of "lymphadenoma cells" was that by Virchow, in 1864; Langhans, in 1872, described giant cells in lymphogranuloma. In 1878, Greenfield noted and drew large multinuclear cells but did not go further, although he had unquestionably discovered the distinctive histologic picture. Goldmann, in 1892, pointed out the frequency of local eosinophilia in the nodes. Sternberg, in 1898, described the characteristic cell which bears his name and laid the foundations for the histologic recognition of the disease. Andrewes, simultaneously with Reed, in 1902, gave the first full description of the histologic appearances. It is well known that Hodgkin's original 7 cases described in 1832 were not all instances of true lymphogranuloma. Fox examined the data on these cases, finding only 3 in which he could consider the condition to be lymphogranuloma as it is known today. In the remaining cases the disease was tuberculosis, syphilis or leukemia. Furthermore, of Wilk's 13 cases, Fox considered only 5 as instances of true lymphogranuloma.

The classic histologic process of Hodgkin's disease is generally described as a progressive diffuse granulomatous (or neoplastic) process, beginning with lymphoid hyperplasia of the lymph nodes, gradual loss of the normal architecture and its replacement with a polymorphocellular tissue, and terminating with the formation of hyaline fibrous tissue. In addition, variations in this general picture are recognized, especially in atypical and borderline cases, in which diagnosis may be difficult or even impossible.

The first histologic change observed is a proliferation of the cells covering the reticulum of the sinuses and of those of the germinal centers (Reed; Simmons), formation of nodules by proliferation of the endothelium of the lymph channels and the capillaries (Sternberg; Coronini) or hyperplasia of the lymphoid cells and of the cells of the germinal centers (Longcope; Fabian; Lemon and Doyle; Symmers). Terplan and Mittelbach did not consider lymphocytic hyperplasia a feature of typical lymphogranuloma, and they called attention to the overgrowth of reticulum cells in the earlier stages.

The ensuing progressive changes appear to vary not only in different nodes but in the elements composing the nodes, according to different investigators. These changes, however, consist in replacement of the normal lymph node structure by a polymorphocellular tissue composed of varying quantities of lymphocytes, endothelial cells, eosinophils, polymorphonuclears, plasma cells, fibroblasts, reticulum, epithelioid cells, megakaryocytes, Langhans' giant cells, myelocytes, myeloplaxes and Sternberg-Reed cells (or lymphoblasts). Certain of these may preponderate, giving more of a sarcomatous picture; in other cases the

cellularity may be greatly decreased, the picture being that of fibrous tissue with a few scattered polymorphic cell nests. The latter appearance is commonly ascribed to the last stage of the disease. Any or all of these pictures may be present in a single node or chain of nodes, which is a point of practical diagnostic importance. Cunningham advised the resection of several nodes in order to avoid confusion in histologic study and diagnosis. Barron also emphasized this. The cases of Sabrazès illustrate the occurrence of mixed histologic pictures.

Before considering several of the more detailed phases, it may be well to review the modern aspects of histologic diagnosis. The criteria necessary to establish a diagnosis of Hodgkin's disease are hardly standardized or uniform, and the apparently increasing inclination of some writers to submerge all or many neoplastic or neoplasmod structures of lymphoid origin under the enveloping and unqualified term "lymphoblastoma" has further complicated the problem.

In the earlier, immature stages of the disease diagnosis may be impossible, as there is nothing entirely characteristic. Later, after the appearance of the polymorphocellular picture, it may be easy. Twort emphasized that the presence of "lymphadenoma cells" (Sternberg-Reed cells) is always necessary for a certain diagnosis, and that with mitoses in several kinds of cells, *débris* necrosis of a particular type, the presence of eosinophils and general loss of architecture are strong supporting points. He stated that mitotic figures in endothelial cells are of great importance, as it is exceptional to find them in chronic lymphadenitis; the same is true of mitoses in fibroblasts and lymphocytes. The usual mitotic figure in lymphogranuloma is like an irregular bundle in the center of the dividing cell; this distinguishes the condition from lymphosarcoma, in which the figures are club-shaped. No single feature can be used as a criterion for certain diagnosis. Sternberg recently stated his concept of the histologic picture—a polymorphocellular granulation tissue, containing lymphocytes, plasma cells, epithelioid cells, frequently eosinophils and especially the large mononuclear or multinuclear cells with abundant cytoplasm and large round, oval or variously shaped, darkly staining nuclei, either lobate or not, and darkly staining. He held that the diagnosis cannot be made without the presence of these cells. He also considered characteristic a regressive tendency of the granulation tissue, with focal necrosis and areas of fibrosis or hyalin. L'Esperance's basis for diagnosis consists in the presence of peculiar myeloid giant cells, endothelial cells, lymphocytes and fibrosis. Hansmann gave particular attention to the filling in of the hilus with solid lymphoid tissue, destruction of the architecture and obscuring of the reticulum of the lymph nodes. "This leaves a lymphomatous mass without any regard for physiologic function in the arrangement of the lymphoid element." Both gross and microscopic studies are

necessary. Hansmann found the well formed Sternberg giant cell frequently lacking. Mallory and other exponents of the lymphoblastic nature of the disease naturally insisted on the presence of the lymphoblast (Sternberg-Reed cell); these cells may be many or few, but they are always present in affected nodes. Medlar, in offering his theory as to the megakaryoblastomatous nature of the disease, expressed the belief that "it is essential to have a pleomorphism of cells which represent the developmental cycle of the megakaryocyte" and that neutrophilic or eosinophilic infiltration or fibrosis is not necessary for a positive diagnosis. Vasiliu and Goia found the Sternberg cell indispensable in making the diagnosis. These cells are not constant in all foci and may be lacking in many. Sweany based the diagnosis on "the gradual spreading type of lymph node tumor that reveals microscopically: diffuse hyperplasia of the lymph node reticulum with varying numbers of bone marrow type of giant cells, and similar types of cells in liver, spleen or lung metastases (when present)."

Boyd pointed out that the picture varies according to the stage of the disease but that ultimately the characteristic changes are seen. Following an early lymphoid hyperplasia, there is replacement by a proliferation of reticulo-endothelium, with the formation of masses of pale cells with pale vesicular nuclei. In addition, there are the lymphadenoma cells (of Reed), which are described as large cells having from four to ten crowded nuclei with dark nucleoli. Eosinophils are rarely absent and "in none of the other pathological conditions affecting the lymph glands are they present in any numbers." Fibrosis may or may not be present. McJunkin held that large mononuclear and multinuclear cells, with vesicular nuclei containing one or more nucleoli, are the characteristic histologic feature. Power and Hala described the usual pleomorphism, but stated that endothelial hyperplasia is invariably absent.

Occasionally the diagnosis "atypical Hodgkin's disease" is encountered, both in the literature and in practice. Under this uncertain designation are placed various unrecognizable conditions, lesions of the lymph nodes that do not fall easily into any other diagnosis and a few cases of true Hodgkin's disease with unusual histologic features. Sternberg recently considered this important question and maintained that in this use of the term physicians have actually gone backward in their knowledge. He further criticized the occasional tendency to arrive at a diagnosis "by exclusion." Abrikossoff called attention to the same trend.

The occasional similarity of Hodgkin's disease to other conditions will continue to cause confusion until the etiology of the disease has been demonstrated. Mention of this problem has been made with

reference to chronic hyperplastic tuberculosis (Karsner), certain thymomas (Ewing), nodes in glandular fever (Baldrige, Rohner and Hansmann; Sprunt and Evans; Longcope), hyperplastic chronic lymphadenitis (Terplan and Mittelbach) and hyperplasia of the giant lymph follicles (Brill, Baehr and Rosenthal). Karsner commented on a form of lymphatic tuberculosis which produces a histologic picture much like that of Hodgkin's disease, but is separable by careful examination; he suggested that this may have caused confusion in those cases which appeared to confirm Sternberg's findings. Metastatic carcinoma may occasionally produce a curious reaction which for a time at least closely simulates Hodgkin's disease. In conclusion of this all too brief discussion of atypical lymphogranuloma, it may be helpful to quote from Sternberg: "The diagnosis of atypical lymphogranuloma has come to mean about as much as pseudoleukemia, into which everything was placed that did not fit elsewhere. This is a pitiable back-step."

The reticulum was studied by Foot, who found the amount variable. In some nodes there is a great deal of new reticulum, and in others practically none. It is usually borrowed from the native tissue of the invaded node and becomes transformed into collagenous tissue. The reticulum in Hodgkin's disease behaves as one would expect it to do in a granuloma rather than as in a tumor.

The reticulo-endothelial system has been prominently mentioned in relation to Hodgkin's disease, especially by Piney, who called the disease a reticulo-endotheliosis. Jaffé found the epithelioid cells of lymphogranuloma similar to those of tuberculosis (Doan and Sabin). McJunkin traced the Sternberg-Reed cells to the reticulum cells. The relationship can hardly be considered as established at the present time.

Vital and supravital staining have been tried. McJunkin stated that reticulo-endothelial cells react characteristically with neutral red, forming spherical aggregations of the dye in the cytoplasm. From the results of injections into lymphogranulomatous lymph nodes he concluded that the Sternberg-Reed cells are derived from reticulo-endothelium. He further stated that "the large hyperchromatic nucleus with a relatively small cytoplasmic mass of dye granules points to a local multiplication by mitosis which is rapid in comparison with that of the same kind of cell in epithelioid tubercles."

Sabin stated that nodes from early cases, when stained supravitaly, show many epithelioid cells characteristic of those found in tuberculosis. Fox found a certain number of rosette cells in nodes stained with neutral red (intravital stain). Janus green showed no structures comparable to mitochondria. Injections of lampblack showed no specific cellular ingestion. Latta and Schulz described the reactions of lymph nodes in general to intravital staining. Laidlaw offered a method for

differential staining of ectodermic and mesodermic cells by silver and described the reaction of the Reed cell in Hodgkin's disease.

The experimental production of the typical histologic picture of lymphogranuloma has not been accomplished, although some writers have described reactions more or less closely approximating it. Bunting and Yates believed that they had reproduced the lesion by the injection of their diphtheroid bacillus. Grumbach described reactions from the use of benzene and of tar. Partial reproductions, such as the development of cells resembling those of Hodgkin's disease, have been described in several papers (Benzançon, Weissmann-Netter, Oumansky and Delarue).

Freifeld described an unusual lipid cell hyperplasia in lymphogranuloma—peculiar groups of light, foamy cells embedded in typical lymphogranulomatous tissue, suggesting a localized xanthomatosis and a possible relationship to Niemann-Pick and Gaucher diseases. Sternberg criticized the diagnosis in his paper on atypical lymphogranuloma.

Invasion of the capsule has been described thoroughly (MacCallum) and may be taken as a fact. Reed did not at first believe in this.

The occurrence of Charcot-Leyden crystals may be marked at times, according to Niçol. Simonds suggested that their presence is related to the local eosinophilic infiltration. Ziegler found the crystals in fresh tissue. Mayr and Moncorps, by a special technic, demonstrated them in suspensions of normal eosinophils.

Necrosis is reported both as frequent (Kusunoki) and as rare (Cunningham). It differs from the necrosis of tuberculosis in that the dead tissue retains its essential structure (Kraus, Lubarsch). Andrewes, as well as Yates and Bunting, believe that it indicates a secondary infective process. Cunningham commented on the association of areas of necrosis and possible anaphylactic phenomena, citing the work of Blumer, who caused lymphatic necrosis in guinea-pigs by the injection of emulsions of nodes from a case of status lymphaticus, and also the work of Woltman, who obtained similar effects by injections of foreign serum. Bierich, Galloway and Urchs suggested that "resorption of partially disintegrated protein from these areas of necrosis may give rise to anaphylactic phenomena." Interference with the local circulation by granulomatous involvement represents the views of Hauck, Chiari and Tsunoda. Twort cited 17 of 61 cases as showing *débris* necrosis.

The effects of radiation therapy on the histologic picture of lymph nodes were considered in some detail by Fox and Farley, who gave a general summary of the pioneer work by Heineke, Pusey and Senn, and Warthin and the confirmation and amplification by David and Desplats, Pancoast, Clarke, Murphy and others. Briefly summarized, the findings are: After irradiation changes may be perceptible almost immediately in the blood, but they are best seen in the glands after

several days. Mild doses produce a low grade hyperplasia in the cords and follicles, while larger doses or repeated exposures are followed by diminution of the number of small mononuclears. After repeated doses large cells resembling lymphoblasts appear. If the irradiation of normal nodes is not too prolonged, the normal architecture returns, but this is not so in the case of pathologic nodes. The reactive phenomena may be stated as an increase in lymphoblasts and endothelial and fibrous tissue. In Hodgkin's disease in particular, there is extensive disappearance of mononuclears, with fibrosis and a reduction in the number of lymphocytes. The tuberculous and the Hodgkin type of granulomatosis belong together, reacting to roentgen irradiation differently from the leukemic and neoplastic hyperplasias. "Tumor cells degenerate readily and completely alter their shape, while lymphoblastic cells retain nearly normal proportions and may vary little or none in staining qualities." Nakahara described the changes in lymphoid organs after roentgen treatment. Isaacs found that myeloblasts and lymphoblasts were stimulated. Simmons and Benet could find no change due to radiation therapy.

The subject of eosinophilia of the nodes has been covered by numerous writers. Goldmann, in 1892, first noted eosinophils; he believed them to have been withdrawn from the blood, a view more recently stated by Symmers. The latter believed that the etiologic agent reacts on the marrow, giving rise to the proliferation of lymphoid type cells, eosinophils and eosinophilic myeloplaxes. These reach the nodes via the blood stream. Barron felt that the presence of eosinophils in the nodes is probably coincident with an eosinophilia of the blood stream. Montgomery suggested the possible significance of eosinophilia in tissue as pointing to involvement of bone. Regarding its value in diagnosis, opinion is divided, and as Simonds stated, "Düring's view is a reasonable one to adopt, namely, that while eosinophiles are not peculiar to Hodgkin's disease, there is no other condition in which they are found in such numbers." The general aspects of eosinophils and immunity are covered by Hajós, Woltman and Ringoen. General articles of value include those of Maximov, Downey and Simonds.

Giant cells in lymphogranuloma have been variously described and named. As already stated, Virchow, in 1864, noted large, peculiar cells, that were later strongly emphasized by Sternberg, in 1898, and by Andrewes and by Reed, in 1902, as of prime importance in the specific picture.

Vasiliu and Goia classified the Sternberg cells into at least two types—the plasmocytic and the reticulo-endothelial varieties. The plasmocytic type is characterized by a clear vesicular nucleus, poor in chromatin, with a large nucleolus (the illustrations show a close resemblance to the typical Sternberg-Reed cell). The reticulo-endothelial type

resembles a multinucleated reticulo-endothelial cell (the illustrations show some resemblance to the megakaryocyte). In the plasmocytic type, all transitions from the plasmocyte to the Sternberg cell may be seen. These authors also noted megakaryocytes and myeloplaxes of the bone marrow type. Carballo described a case of a sarcoma-like, plasma cell lymphogranuloma with a large plasma cell as the predominating type. Lange believed that the Sternberg cell arises from the adventitia, a view held by numerous others (Catsaras-Georgantas; Kirchner; Terplan; Russell; Warneke; Marchand). Mallory's well known view that this cell is a lymphoblast is, of course, held by those who feel that the disease is a lymphoblastoma. Medlar suggested the possibility of the identity of the Sternberg cell and the megakaryocyte, and this forms the basis for his theory of the megakaryoblastomatous nature of the disease. Medlar's views are possibly the most recent development in the field of the probable nature of the disease.

In studying the literature on the Sternberg cell, also called the Dorothy Reed cell, rather different descriptions were encountered, which are not easily reconciled. The cell described in Sternberg's original paper, in 1898, has abundant cytoplasm and one or more large, variously shaped nuclei which stain intensely. His illustrations clearly show this form. Reed's description and illustrations are different. She depicted a large cell with a large pale nucleus or nuclei showing a prominent chromatin network and prominent nucleoli that take a contrasting stain. The cytoplasm shows irregular protoplasmic processes. The question as to the relationship of these cells remains unsettled, but certainly the two descriptions would indicate the existence of two types of the so-called specific giant cells. Cases are continually encountered that show a preponderance of one or the other of these types. Haythorn, Robinson and Johnson described a case of Hodgkin's disease in which the patient was secondarily infected with a monilia. The reaction in the areas infected with the monilia as well as in the Hodgkin's nodes showed typical Dorothy Reed cells, and this suggested that "these cells are wandering cells which may respond to inflammatory stimuli outside of the Hodgkin's nodules, just as other wandering cells and blood elements are capable of doing."

Giant cells of the Langhans type are mentioned by several authors (Reed; Karsner; Longcope). Karsner differentiated the giant cells of hyperplastic tuberculous lymphadenitis from those seen in Hodgkin's disease in that "the former show relatively solid nuclei, and the latter distinctly vesicular nuclei." Haythorn, in an extensive review of multinucleated giant cells, considered both the Reed type and the foreign body type. He stated that the two are apparently constantly associated in Hodgkin's disease as well as in lymphoblastic tumors, but are not related in origin.

Goldmann described "Kugelzellen" in Hodgkin's disease, and these were considered by Reed. With Ehrlich's tri-acid stain they appear as large cells with a golden-red cytoplasm made up of large, irregular droplets with a small, indefinite nucleus. Carballo reported on the occurrence of pleokaryocytes (hyperlobulated forms of polymorphonuclears), stating that he found them locally but not in the peripheral blood.

Finally, the megakaryocyte, to which Medlar called attention, must be considered. Reference to Medlar's original paper should be made for the details of his views on the megakaryocyte and its ancestors. Meyer stated that megakaryocytes exist in normal lymph nodes, more profusely in the fetus than in the adult human being. Aschoff said that their naked nuclei are frequently lodged in the capillaries of the lungs. Minot held that these cells usually block the further passage of the normal megakaryocytes and that consequently those seen in the peripheral circulation are most commonly fragments or nuclei. Watson discussed their presence in the blood, the spleen and the liver in a case of splenomegaly with anemia. Körner and Minot described cases of myelogenous leukemia with numerous megakaryocytes.

GENERAL BLOOD PICTURE

Attempts to formulate hematologic criteria for the positive diagnosis of Hodgkin's disease have not been successful. Bunting claimed that such a diagnosis is possible, and he has made it on several occasions (Yates). McAlpin could not substantiate these claims, and most observers have agreed that the findings are neither typical nor constant.

Unfortunately, in many cases there is only a single blood count, taken at random. Fabian, in 1911, insisted on numerous counts. Bunting used counts based on at least 500 cells and made them himself, feeling perhaps that the average technician is hardly qualified to make the exact determinations necessary or to gain the mental impression that only a personal and expert examination gives.

It is hardly necessary to refer to the changeable clinical course, the profound effects of radiation therapy, the effects of diet and metabolism, the influence of localization, especially regarding the hematopoietic system, and the possibility of secondary infections. All of these and more must be considered in relation to the blood picture and its interpretation.

There seems to be a definite trend toward attempts to obtain type blood formulas in relation to preponderating localization and course. Thus Favre associated pruritus with eosinophilia. Hayden and Apfelbach reported that in cases involving the gastro-intestinal tract there was generally a normal or a low white cell count in the presence of fever,

secondary anemia, actual lymphopenia or slight eosinophilia. When the spleen was affected, Rolleston and also Weber found leukopenia with lymphocytosis. Weber also suggested that in cases of very high eosinophilia the intestine was invariably involved. Eosinophilia as a specific reaction of the bone marrow was noted by Stewart. Montgomery's work was in agreement with this; he suggested a search for involvement of bone in the presence of definite eosinophilia.

Barron suggested the possibility of confusion of Hodgkin's disease with typhoid or with relapsing fever in the presence of leukopenia in the more acute cases with prolonged high fever. The similarity is close, especially in cases without externally visible lymphadenopathy. Numerous observers have made use of the blood count in differential diagnosis, especially in relation to the leukemias; this is a finding of value.

The following opinions as to the general findings in the blood are briefly abstracted: Bunting noted in cases of less than one year's duration that there was no leukocytosis but that relative lymphocytosis occurred, as well as an increase in transitionals and a decrease in eosinophils. McAlpin could not confirm this, but Falconer did, adding that later in the course there may be leukocytosis, with polynucleosis, a fairly constant mononucleosis, no elevation of the platelet count, and an eosinophil count usually about normal or lower, but occasionally very high. Muller and Boles noted an early lymphocytosis followed by polynucleosis and an increase in transitional cells and platelets (findings which in general agreed with those of Bunting). Fox found polynucleosis, a normal lymphocyte count, early anemia and a chronic course. Schreiner and Mattick noted secondary anemia, leukocytosis, polynucleosis, moderate eosinophilia and an increased platelet count, an increase in the transitional cells not being commonly present. Straube reviewed the literature and contributed 21 cases of his own. He held that there is no uniform and specific blood picture, and that the condition cannot be diagnosed on the basis of the findings in the blood.

The most common and constant finding seems to be a relative and absolute moderate polynucleosis with lymphopenia. Aubertin in 100 observations found this lacking but 9 times, and he considered leukopenia absolutely exceptional when radiation therapy has not been used. Vasiliu and Goia reported that an elevated leukocyte count may indicate a malignant trend. Baldrige and Awe believed the sclerosing type of lymphoma to be the most frequent cause of a nonleukemic leukocyte count of 20,000 or more in a patient free from fever. Bunting and Yates have long held that leukocytosis occurs later in the course. Rolleston did not find leukocytosis, but rather a normal count or leukopenia. Klima studied 32 cases and came to the conclusion that in the early stages or in remissions the count was normal; in chronic generalized

lymphogranuloma or when tumor-like masses were present, there was an increase in neutrophils and monocytes or a progressive lymphopenia, and rarely eosinophilia; the red cells were normal or moderately decreased in number; in the rapidly progressing cases, there were severe anemia, neutropenia and progressive lymphopenia or eosinophilia, and marked lymphopenia seemed to be a sign of a rapid course.

Leukopenia may be very marked (Gütig; Meyer; Mellon; Urchs; Jaffé; Miller). Miller cited a case in which the leukocyte count was only 240. Moderate leukopenia (a count below 6,000) was reported in a small percentage of cases (Ziegler; Fabian; Barron; Miller [who also gave a special bibliography]). Simmons and Benet never found leukopenia. Weber reported that it is not uncommon in the advanced stages of the disease. Bine described progressive leukopenia. Fox and Farley also discussed leukopenia. The leukocyte count may be normal, not only at odd times but during the entire course of the disease (Miller; Fabian; Ziegler).

The leukocyte count may be oscillating. Thomson described a remarkable daily fluctuation of from 6,000 to 75,000. Another case of his showed a variation of from 6,000 to 66,000 in twenty-four hours. In a case of cancer he found a daily variation of from 5,000 to 40,000. Simmons and Benet cited a case in which the percentages of polymorphonuclears and lymphocytes were reversed. Fabian's insistence on repeated counts hardly need be emphasized under these conditions.

Hematologic Effects of Irradiation.—As the roentgen rays have played so extensive a part in the therapy of this disease, and as their effects are profound, not only on the actual lesions but on the general organism, it is important to consider the blood picture as it is affected in the course of such treatment. Minot and Spurling investigated this subject extensively with human and animal blood and found that exposures to roentgen rays of short wavelength produce a definite and somewhat persistent leukopenia, which is in proportion to the dose used. "Coincident with the drop in the lymphocytes, the polymorphonuclear eosinophiles undergo a decrease—later they may increase over a period of days to weeks, reaching often above normal and sometimes as high as 15 per cent, then returning to normal in a similar period of time." They summed up the usual course of events as: (1) transient leukocytosis; (2) leukopenia lasting from nine days to four weeks, with lymphopenia, the leukocyte count being still further depressed if treatment is given before the return to normal; (3) eosinophilia, with a count of from 7 to 23 per cent, from two to three weeks after exposure; (4) the appearance of degenerated cells, especially during the first three days; (5) a slight increase in platelets.

Fox studied the influence of the roentgen rays on the polymorphonuclear count: These cells were increased and were not influenced

by roentgen irradiation, whereas in the leukemic group the polymorphonuclears were few and were sensitive to the roentgen rays.

The peculiar sensitiveness of lymphoid cells to the roentgen rays was first brought out by Heineke. Taylor, Witherbee and Murphy studied the effects of roentgen irradiation on several types of animals and found that there is a sharp fall in the lymphocyte count during the first two days, followed by a slight rise and then another slight fall which is followed by a final rise. They also found that in 7 of 9 rabbits lymphocytosis could be produced by small doses of roentgen rays. Portis, examining the blood picture shown by workers with x-rays, found leukopenia with lymphocytosis and occasional myelocytes. No change was noted in the red blood cells and platelets. These results appear to be in accord with those of Taylor and his associates.

Isaacs considered the mechanism involved in the roentgen treatment of leukemias and lymphomas. He stated that the roentgen rays stimulate primitive myeloblasts and lymphoblasts to rapid reproduction. Myelocytes and small lymphocytes are stimulated to finish their life history; they then die or are excreted, very rapid excretion resulting in a leukopenia which gives the false impression of an aplastic bone marrow. Anemia may mean crowding out of the red blood cells by foreign cells, or it may mean actual aplasia of the marrow.

Shawhan discussed the hematologic response to irradiation in a case of Hodgkin's disease; he found essentially a return to a much more normal count than was shown before treatment. Burnam noted the same in many cases. Simmons and Benet have noted that radium treatment reduces the lymphocyte count in Hodgkin's disease, the maximum effect being seen in about two weeks. Krantz agreed. Weber called attention to the possible influence of prolonged roentgen therapy in producing a lowered polymorphonuclear count and anemia.

In summary, the blood picture in a case of Hodgkin's disease in which radiation therapy is used will depend not only on the disease process itself but on the several factors involved in the effects of radiation therapy. This must be held in mind in attempting any evaluation of the blood count in this disease.

Erythrocytes and Hemoglobin.—Moderate progressive anemia of the secondary type is the rule, the degree varying in different cases. Piney stated that "the absence of any great degree of interference with erythropoiesis is to be expected in a malady in which the essential feature is formation of hyperplastic reticuloendothelium, which is an extra- rather than an intra-vascular process." Barron described the anemia as of the cachectic type and present in all cases in the last stages, though it may occur early. The hemoglobin averaged from 30 to 60 per cent; in one case it was but 19 per cent. Burnam stated that

the anemia is usually not profound, the average hemoglobin value being about 70 per cent, and that poikilocytosis, polychromatophilia and nucleated red cells are exceptional. Straube attached small importance to the anemia. Halix stated, however, that early in the course there may be severe anemia, which may closely resemble pernicious anemia. Piney stated that at times erythroblasts appear in small numbers; their occurrence is common in advanced cases involving the bone marrow. Borsutzky found severe secondary anemia in all cases in children. He observed no hemorrhagic diathesis in children. Baldrige and Awe cited a case in which there was simulation of aplastic anemia, with enlarged spleen and without enlarged lymph nodes until six days prior to death. The bone marrow in this case was replaced by the characteristic tissue of Hodgkin's disease. Laur found the reticulocytes to be increased to from 5 to 13 per cent; he concluded that there is a spontaneous reaction in the marrow like that in pernicious anemia.

In summing up the data and forming a general impression, it may be stated that all cases show some degree of the cachectic type of secondary anemia; in scattered cases the anemia is of greater intensity, and in some instances it simulates either pernicious anemia or aplastic anemia, which is important in differential diagnosis.

Platelets.—Bunting held that the platelets are constantly increased in number and size; some of them are very large, being practically megalokaryocytic pseudopodia. He explained occasional low counts by the suggestion that there is an eventual necrosis of megalokaryocytes in the marrow, with resulting failure to form platelets. In one of his cases there were enormous pseudopodia-like masses (50 microns long) which he believed to be masses of megalokaryocytic protoplasm and their unconstricted pseudopodia, the remains of megalokaryocytes stripped of their protoplasm after passing through the lung from their point of origin in the bone marrow. McAlpin (using Ottenberg and Rosenthal's method of counting) found high platelet counts in 7 of 18 cases. Falconer did not find the counts high, although in general his results agreed with those of Bunting. Vasiliu and Goia, Cunningham and Burnam did not find an increase in a majority of cases; Miller and Boles found increased counts, as did Schreiner and Mattick.

In evaluating platelet counts a number of factors must be considered. Several papers have an indirect bearing on this. Bannerman, following the work of Bull, Delrez and Govaerts, and Cramer, Drew and Mottram, had reason to believe that platelets are concerned in resistance to bacterial infection. He was able to show that there is a general relationship between the body temperature (as in pyrexia) and the number of platelets in the blood; the two are parallel. He also indicated that the amount of exercise taken and the time of day when the

determination is made may affect the count. Bedson's work on the rôle of the reticulo-endothelial system in the regulation of blood plates showed that reticulo-endothelial blockade by particles of carbon is associated with a considerable increase in the number of circulating platelets. Koster noted the same association; he observed also that following the increase in platelets there is a sharp recoil, followed by a gradual diminution, even though the blockade is maintained. Bunting's idea concerning the platelet count may thus be justified. It seems hardly necessary to allude to the belief of many that the reticulo-endothelial system is deeply concerned in lymphogranuloma, and the speculation is interesting that perhaps these same factors are operative to some extent in this disease.

Lymphocytes.—Ziegler's statement that the lymphocytes are usually relatively and absolutely decreased has the support of numerous observers and is in keeping with the polynucleosis frequently encountered. Fabian stated that the lymphocyte count may be low—from 0 to 3 per cent—and that lymphopenia most frequently accompanies an absolute increase in the number of leukocytes, may occur at times in association with reduced leukocyte count, and is seldom noted when there is a normal leukocyte count. He also found at times a moderate relative lymphocytosis of transitory nature. Bunting gave a reduced percentage, with more marked reduction in the later stages. Muller and Boles found generally an early lymphocytosis with later lymphopenia. Terplan and Mittelbach stated that moderate leukocytosis with lymphopenia is the rule. Vasiliu and Goia found that 5 per cent of cases show lymphocytosis. Hayden and Apfelbach, Cunningham, Borsutzky and others stated that a majority of cases show lymphopenia. Straube divided his cases according to the relationship between the number of lymphocytes and the total white cell count. In the early forms there is lymphopenia with a normal leukocyte count; when complications are present, lymphopenia with leukocytosis, and in generalized and abdominal forms, lymphopenia with leukopenia. Hayden and Apfelbach's conclusions regarding the lymphocyte count in cases involving the gastro-intestinal tract are in agreement with Straube's third conclusion, that in abdominal (gastro-intestinal) forms there is lymphopenia with leukopenia.

Some cases show lymphocytosis, which is rarely pronounced. Fabian believed that lymphocytosis is usually moderate and transitory. Jaffé reported a case of lymphogranuloma of the intestine with extreme lymphocytosis (1,000 white blood cells, with 89 per cent lymphocytes). Gutig's case (cited by Ziegler) showed a rise in the proportion of lymphocytes of from 22 to 99 per cent just prior to death. The total leukocyte count was 2,000. Rolleston felt that usually there is leuko-

penia with relative lymphocytosis, especially when the spleen is involved. Weber agreed with him. Simmons and Benet stated that the lymphocytes are usually somewhat increased; they mentioned the effects of radium in producing a reduction in lymphocytes. Fox stated that the proportion of lymphocytes is usually normal. The effects of radiation on the lymphocytes must not be forgotten; this is given consideration under another heading.

Transitional Cells.—As Bunting has placed so much emphasis on the transitional leukocyte, his description is given: The nucleus stains sharply with Wright's stain; it is massive and of several shapes—knobbed, lobed, twisted, folded or ring-shaped. It may be so complex that it suggests a foreign cell. The protoplasm is clear blue, crowded with azure granules finer than those in a polymorphonuclear and of the same tint as those in platelets.

The normal percentage as given by different authors varies considerably: Bunting gave from 2 to 8; Wood, 2 to 4; Webster, 3 to 5; Gulland and Goodall, 3 to 10, and Naegeli, 6 to 8. McAlpin stated that, to be considered high, the count must be at least 5 per cent, which is a fair estimate.

Bunting's findings are that in Hodgkin's disease with a normal leukocyte count the transitional cells average about 10 per cent; with leukocytosis they average 6.4 per cent (a reduction) and with leukopenia they average 17.8 per cent (an increase). This indicates that there is a relatively large number of transitionals in the circulation throughout the disease. McAlpin's figures did not corroborate this; only 8 of 18 cases showed an increase in transitional cells. Burnam's large series of cases showed no increase in a majority of cases. Cunningham found the proportion variable, but in general increased. Schreiner and Mattick did not find an increase in transitional cells commonly, and Miller's figures were also low. Symmer's cases showed a uniformly low count. Muller and Boles stressed an increase in transitional cells.

Briefly summed up, the percentage of transitional leukocytes is variable. It is suggested that Bunting's description be used in future work in order that more uniform and dependable results may be obtained, for the constitution of a transitional cell is variously interpreted and it may be that the variable results can be traced to that source to some extent. If reliable figures bearing on Bunting's theory are to be obtained, certainly more expert identification is necessary than can be made by the average intern, whose results on such critical points are so frequently taken by authors in working up their cases.

Cunningham found 13.3 per cent transitional cells in a case of primary large round cell sarcoma of the mediastinum. He called attention to the probability of mistakes if Bunting's ideas are to be relied on.

Megalokaryocytes.—Bunting and others have seen these cells in the blood. Minot reported immature forms as present. They are undoubtedly rare.

Mast Cells.—Fabian, Rulison and Symmers (case 12, 5 per cent) have noted mast cells in rare instances.

Polymorphonuclear Neutrophils.—Fabian's statement that the most frequent change in lymphogranuloma is an absolute polymorphonuclear neutrophilic leukocytosis is concurred in by many observers, among whom may be listed Dimmel, Cunningham, Rauke, Muller and Boles, Bunting, Piney, Schreiner and Mattick, Burnam, Ziegler, Desjardins and Ford, Terplan and Mittelbach, and Falconer. Falconer agreed with Bunting that this is apt to occur after the first year of the disease. Simmons and Benet noted that three fourths of his cases showed an increase. From an estimate based on the compiled cases as well as on personal observation I believe that the great majority of elevated percentages fall between 68 and 85 per cent. The percentage may also, though uncommonly, be very low; Jaffé's case showed a total white blood cell count of 1,000, with 89 per cent lymphocytes. The increase in polymorphonuclear neutrophils has so frequently been noted that the conclusion may be justified that it commonly occurs, not in all cases, but in the majority.

Eosinophils.—An occasional case shows a very high proportion of eosinophils, a finding by no means constant, the higher percentages being rare. Baldrige and Awe found 83 per cent eosinophils in a case in which the total leukocyte count was 43,800. Rolleston cited 2 counts of 26 per cent and 69 per cent; Gysi found 67.5 per cent (white blood cells, 32,000). The usual percentage of eosinophils is much lower, being from 4 to 6 per cent in about 25 per cent of all cases, and normal in the others (Fabian). As regards the value of the eosinophil count in diagnosis, MacNalty, Dreschfeld and Barron held that the presence of eosinophils in association with enlarged lymph nodes helps materially in establishing the diagnosis. Terplan and Mittelbach believed that eosinophils play no rôle. Bunting stated that the percentage is low in the active stages and normal or slightly higher in the reactive or quiescent stages, and that it may form an index to the activity of the disease.

A possible association between eosinophilia and pruritus has been discussed by several authors. Favre insisted on a constant relationship between the two. Rolleston, however, cited 2 cases to controvert this: In the first there were 26 per cent eosinophils without pruritus, and in the second (E. Bellingham Smith's case), 69 per cent eosinophils without pruritus, although the patient in the latter case had some itching

earlier in the course, the count at the time being 39 per cent. Such observations occur in the examination of any large series of cases.

Klauder, Weber and Bode, and Stewart believed eosinophilia to be an expression of the allergic state. Barron expressed his belief in the possibility that Hodgkin's disease is of animal parasitic origin, such diseases being generally accompanied by eosinophilia. Montgomery suggested that involvement of the bone or bone marrow is to be looked for in the presence of eosinophilia; Weber and Bode, that the intestines are involved. Stewart, after careful study of a case of familial eosinophilic diathesis plus Hodgkin's disease, stated that "eosinophilia in the majority of cases is a specific reaction of the bone marrow in Hodgkin's disease." He also cited the literature on cases of Hodgkin's disease with hyper-eosinophilia. In concluding, he stated that the exaggerated eosinophilia in his case was apparently due to a well established familial allergic background (asthma and eczema), to a familial eosinophilic diathesis, to a personal allergic background (asthma in childhood), to the specific eosinophil-stimulating effect of Hodgkin's disease and to the added effects of arsenic therapy. Holzkecht cited 2 cases presenting eosinophilia. Page, Turner and Wilson brought the broader aspects of the problem to attention in an examination of 5,500 general medical cases, in 300 of which eosinophilia was present. The eosinophilia was associated with parasitic infections in 10 per cent of the cases, with rheumatic fever in 13 per cent, with chronic pulmonary disease in 13 per cent and with chronic nephritis and arteriosclerosis in 10 per cent; in fully 40 per cent, it occurred in isolated cases of various conditions and had no diagnostic significance.

The work of Meulengracht and Holm must also be given consideration, particularly because liver has been rather widely used in the treatment of all types of anemia by physicians in general. They stated that eosinophilia sometimes appears suddenly in the course of treatment of pernicious anemia with liver and persists as long as the administration of raw liver is kept up. Fried liver rarely produces this phenomenon. As controls they used patients with other diseases, and the same result was obtained. Such percentages of eosinophils as 20, 40 and even 74 were found.

Griffin and later Harrison reported the occurrence of eosinophilia in association with splenomegaly, and involvement of the bone marrow and lymph nodes. Ringoen discussed the origin of eosinophils. Hajos considered the relationship of these cells to the formation of immune bodies. Schwarz reviewed 2,758 articles on eosinophilia.

Basophils.—Cunningham's 10 cases showed basophil counts of from 0 to 1.5 per cent. Bunting's figures were similar. Basophils are not affected by the disease.

Large Mononuclears.—Cunningham's figures show a variation of from 1.5 to 22.3 per cent (normal, from 4 to 8 per cent); in 7 of 10 cases the percentage was well above the normal, and in only 2, below. Borsutzky noted a decrease in two thirds of his cases in children. Falconer found a fairly constant increase. Bunting found no change in numbers. Straube noted an increase but believed it to be of small importance. Brandt noted an increase only in isolated cases. Piney accepted the contention of Aschoff and Kiyono that the monocytes are derived from the reticulo-endothelial system but qualified his belief by stating that the monocyte is as much a myeloid cell (from the myeloblast) as is any other granular leukocyte.

Myelocytes.—Aubertin found myelocytes occasionally, usually in cases showing marked polynucleosis. Fabian found them at times, with higher percentages exceptional.

RETICULO-ENDOTHELIUM

The reticulo-endothelial system has been brought into considerable prominence, chiefly by Piney, who repeatedly suggested "that Hodgkin's disease is to be regarded as being essentially a proliferation of reticulo-endothelium and its derivatives," and called it a reticulo-endotheliosis. Rolleston, in commenting on Piney's theory, brought out an interesting point—that if the process were primarily a proliferation of endothelial and reticular cells, "Kupffer's cells in the spleen and liver should be constantly and predominantly affected, and this is not the case."

Of practical interest, especially in diagnosis, are a number of papers, most of which are by German writers, on various phases of "reticulosis." In some of the cases described the condition bears such a marked resemblance to true Hodgkin's disease that absolute distinction may be impossible. I had a case in which the condition was diagnosed as Hodgkin's disease by competent pathologists and had many of the characteristics of that disease. The histologic picture, however, could not be considered as quite typical; there was extensive proliferation of large pale cells in the nodes, almost exactly like those in the case of Schultz, Wernbter and Puhl, which showed hyperplasia of the reticulo-endothelial cells together with the formation in several organs of nodules made up of large phagocytic cells. The case of Tschistowitsch and Bykowa was similar; the diagnosis was *reticulosis universalis aleukemica*. These authors recognized that lymphogranuloma in some ways parallels those little known states. Certainly, the differences between a reticulo-endothelial hyperplasia, such as their case presented, and the hyperplastic or active cellular stage of lymphogranuloma are no greater than those separating lymphogranuloma in the earlier stages and a small cell lymphosarcoma.

Tschistowitsch and Bykowa included a good bibliography on the general subject of reticulo-endothelium. Vehlenger, in addition to reporting a case of aleukemic reticulosis, offered a classification of reticulo-endothelial hyperplasia. Jaffé thoroughly reviewed the literature on the reticulo-endothelial system. Watson's review covered the American literature for 1926. Ferrata's work on the blood includes a full discussion of reticulo-endothelium. Further material on reticulo-endothelium and lymphogranuloma may be found in the section devoted to histology.

PORTALS OF ENTRY

Numerous attempts have been made to locate possible points for the entrance of an etiologic agent. The most frequently mentioned portal is the tonsil; an invasion at this point is followed by cervical lymphadenopathy. Cases have followed tonsillectomy (Burnam [5 cases]; R. Paltauf; Simmons and Benet; L'Esperance), other cases have followed acute or chronic lesions around the mouth, throat or ear (MacNalty, otitis media; Taylor, tonsillary abscess; Arkin, chronic tonsillitis; Cunningham, tonsillitis and diphtheria). Carious teeth were mentioned by Desjardins and Ford, who were impressed by the frequency of the relationship between the adenopathy and chronic lesions of the mouth, throat, teeth, tonsils and nasopharynx.

Feer expressed the theory that if the portal of entry were by way of the pharyngonasal cavity, the cervical nodes would be involved; if through the lungs, the mediastinal nodes, and if through the intestinal mucosa, the mesenteric and retroperitoneal nodes. If entry is by way of the intestine, the process spreads through the thoracic duct, particularly to the supraclavicular nodes of the left side, an observation of clinical value. Kraus traced a possible portal to the upper lobe of the right lung by estimating the relative age of the lesions, considering that the ones apparently the oldest were the first to appear. The danger of drawing such a conclusion is evident, because of wide variations in the structure of nodes of the same or apparently the same age. Saupe held that pulmonary foci are not so rare as is commonly maintained. Cunningham observed a case of intestinal origin.

Symmers stated that primary enlargement of abdominal or of abdominal and thoracic nodes combined is 10 times more common than primary enlargement of the cervical nodes. Ewing supported this view, adding that the superficial nodes which first attract attention are merely the outlying portions of an internal lesion. This marks a definite advance in the modern concept of the disease.

Cases following various infections are not rare. Corbeille found that in more than one third of cases in children there was a history of infectious disease at the onset of the typical symptoms. Bunting's case

of involvement of the inguinal lymph nodes followed cystitis. I have seen 2 cases following pulmonary disease (pertussis, influenza). The possible rôle of trauma is considered under the heading of medico-legal aspects.

INVOLVEMENT OF VARIOUS ORGANS

Lungs.—Pulmonary involvement is common, depending to a certain extent on the preponderating distribution of the diseased nodes, i. e., mediastinal or abdominal. Baldridge and Awe reported 14 cases, of which 7 (50 per cent) showed involvement of the lungs. It is probably possible to recognize three types of pulmonary involvement: massive invasion of the hilus by mediastinal enlargements, extensions into the lung proper by radiating bands following the interlobular lymphatics (Simonds), or small isolated nodules scattered throughout. The lung may be replaced by the new tissue, according to Schottelius and Chiari.

H. Weber, in discussing 7 cases of marked pulmonary involvement, called attention to Wohlwill's classification of pulmonary types of Hodgkin's disease: 1. Involvement begins in a bronchus and spreads along the bronchial tree, surrounding it and simulating bronchogenic carcinoma. 2. Multiple nodules of varying size are scattered throughout the lung, grossly resembling metastatic tumor of the lung. 3. The lung is invaded by continuity of a process in the hilar lymph nodes. Lignac described lesions investing the bronchi and vessels in a mantle-like fashion, similar to Wohlwill's type 1.

Other phases are: filling of the alveoli with granulomatous material (MacCallum); tracheo-esophageal fistula (H. Weber); erosion of the trachea and bronchi (MacCallum; Ness and Teacher; Fraenkel and Much; Meyer; Steiger); stenosis of the bronchi (Weber; Ziegler; Ferrari and Comotti); cavitation (Dvorak; Shapiro), and pressure atrophy of the wall of the chest (Lyon). Wessler and Greene noted that enlargement of the right paratracheal nodes occurs frequently in Hodgkin's disease, but uncommonly in other diseases. Terplan's case showed marked involvement on the right side, with an isolated nodule in the apex of the right lung, which he considered to be a primary focus. Bouslog and Wasson described formation of cavities simulating those in tuberculosis, death being due to pulmonary hemorrhage. Cooper's case was unusual, as the patient was 72 years old and showed an acute mediastinal process without noticeable enlargement of the superficial lymph nodes. Other reports of general interest are those of Kuckuck, Albot and his co-workers, and Lignac.

The pleura is occasionally involved (Reckzsch; Yates and Bunting; Hecker and Fisher; Symmers; Lyon), with effusion in some instances (Ziegler; Waetzold; MacCallum; Fabian; McAlpin and von Glahn; Edsall; Weber and Ledingham; Graeka).

The larynx may be involved, according to Chatellier and Halphen.

Liver.—Limitation of the process to the liver is unknown (Rolleston; Muller and Boles), but the liver is generally, though not always, involved in conjunction with the spleen. The following percentages of incidence of involvement of the liver are taken from the literature: Barron, 50; Ziegler, 60; Rolleston, 50; Symmers, 71; Terplan and Mittelbach, 50; Cunningham, 17. On the basis of these figures, the average percentage of cases in which involvement of the liver occurs is about 50. Burnam, speaking of clinically enlarged liver, gave an incidence of but 4 in 173 cases; MacNalty, 1 in 5, and Barron, over 50 per cent. Hayden and Apfelbach stated that the liver and spleen are usually not enlarged in lymphogranulomatosis of the gastro-intestinal tract. Barron remarked that "it is likely that the peribiliary infiltration produces jaundice more frequently than does pressure of enlarged lymph nodes or tumor masses against the large bile ducts." According to Coronini, icterus in lymphogranuloma is obstructive, as a result of: (1) compression of the common duct alone; (2) obliteration of the common duct alone; (3) changes in both the extrahepatic and the intrahepatic ducts; (4) changes limited to the intrahepatic ducts. Obstruction of the extrahepatic bile ducts may be due to pressure by enlarged nodes or to invasion of the duct wall by lymphogranulomatous tissue. Within the liver the interlobular ducts may be compressed by involvement of the interlobular stroma. Symmers found that in his series "the nodular foci arose in the periportal spaces and were initiated by hyperplasia of the lymphoid cells in the walls of the portal veins, followed by the appearance among the lymphocytes of mononuclear and multinuclear giant cells with or without the presence of eosinophiles and eosinophilic myelocytes, the whole supported in a connective tissue reticulum, the nodules expanding in such fashion as to subject the neighboring lobules to atrophy from pressure, but never directly infiltrating them." In one of his cases he found changes essentially composed of great thickening of the intrahepatic portal veins, in the walls of which was the typical lymphogranulomatous process, the connective tissue replacing the organ; he believed that these changes constituted a hitherto undescribed phase of the pathologic process.

Terplan and Mittelbach cited an unusual case involving the liver and spleen (case 22), in which the liver weighed 3,300 Gm. Barron described a case in which the liver weighed 3,000 Gm. Crouzon, Bertrand and Lemaire noted a case with amyloid changes. The simultaneous occurrence of tuberculosis and lymphogranuloma in the form of well defined discrete and separate nodules in the liver has been described several times.

Spleen.—The primary splenic form of Hodgkin's disease is rare, even if such a state is admitted to exist. Opinion is divided on this

point. Ziegler allowed the inclusion of this form. Symmers, L'Esperance, Wade, Mellon, Doncaster, Muller and Boles, and Burnam cited cases suggestive of such a condition; yet in none of these cases can the diagnosis be considered as proved. In Muller and Boles' case autopsy showed involvement of the spleen and bone marrow, without enlargement of the lymph nodes. In the other cases the diagnosis was based on clinical and surgical findings. Larrabee's case, in which splenectomy was done because of an enlarged spleen, can hardly be accepted, as the lymph nodes in the neck were palpable before operation. The patient recovered and was well two years afterward. The greatest handicap in deciding the issue is the lack of adequate autopsies in the cases reported and also the difficulty, if not impossibility, of the determination of the relative age of the individual lesions. The criterion of fibrosis does not hold. The question should remain open.

The majority of writers agree that splenic lesions are common. Barron stated that they are usually miliary or submiliary, with occasional larger masses. The involvement is often observable on microscopic examination, at times being definitely specific and at times only suggestive. Ziegler's estimate that from 65 to 75 per cent of cases show splenomegaly is well borne out by the following compilation of data from the literature: Of 321 cases, 226 or 70 per cent showed some degree of splenomegaly (Murray; Turnbull; Symmers; Muller and Boles; MacNalty; Barron; Cunningham; Terplan and Mittelbach; Clark; Simmons and Benet). The greatest weight noted was that in case 22 of Terplan and Mittelbach, 3,720 Gm. Spleens of normal size or smaller than normal are fairly common.

The spleen in limited gastro-intestinal Hodgkin's disease is not involved as often as one might suppose. Hayden and Apfelbach stated that the spleen and liver are usually not involved, which supports Partsch's statement. In cases in which the gastro-intestinal tract is involved as a part of an abdominal distribution, the spleen is commonly enlarged.

MacNalty made an interesting observation—that the splenic enlargement is more marked in the period of pyrexia, and that the organ may be palpable only at this period. Tenderness or pain in the flank may be due to infarction.

Corbeille, after observing 33 cases in children, stated that splenic enlargement is the most frequent abdominal sign of the disease in children. Holler and Paschkis reported an unusual case in which the clinical diagnosis was hemolytic jaundice and splenectomy was performed. The diagnosis of Hodgkin's disease was unexpected.

Suprarenal Glands.—Involvement of the suprarenal glands is rare. Ziegler had seen no authentic cases. Simmons examined the cases of Yamasaki, Fraenkel and Much, and Paunz. Paunz gave an excellent

description of numerous focal lesions in the suprarenals. Barron mentioned a case but did not go into detail. Bine described a case with extensive destruction of the suprarenals by necrosis, little normal tissue remaining, and without special clinical symptoms.

Enlarged nodes surrounding the suprarenals, practically embedding them in a mass of lymphogranulomatous tissue, are described more frequently. Nieszkowski, Fowler, Bramwell, Symmers and Laporte reported on this aspect. Rolleston believed that the symptoms produced depend on irritation of the sympathetic nervous system rather than on actual involvement of the suprarenals. Symmer's case of *acanthosis nigricans*, in which there was lymphogranulomatous invasion of the celiac plexus without involvement of the suprarenals, supports this view.

Gastro-Intestinal Tract.—Hayden and Apfelbach, in 1927, covered the subject of gastro-intestinal Hodgkin's disease thoroughly, reviewing 26 cases and presenting 3 new ones. They made a special attempt to form a group of diagnostic features suggestive of lymphogranuloma of the gastro-intestinal tract—fever, diarrhea, abdominal pain, rapid cachexia, secondary anemia and leukopenia or a normal white blood cell count. The cases fell into three clinical groups resembling other more common entities—ulcerative enteritis and colitis, particularly the tuberculous forms, gastric carcinoma and intestinal obstruction. They noted that the liver and spleen are usually not enlarged and that nodules in these organs are uncommon. In a few cases the superficial nodes were enlarged, but this was unlike the more common extensive enlargement of generalized Hodgkin's disease. Vasiliu and Goia found the chief clinical symptom to be "dyspepsia," which is worse at night. The patients are supposed to have a gastropathic condition, as the lymph nodes are too small to be noticed on examination. Coronini paid particular attention to the pathology of lymphogranuloma of the gastro-intestinal tract. The lesions may involve this tract exclusively, chiefly or as a part of a generalized process. The lesions may appear as nodules arising in the submucosa which protrude into the lumen and often ulcerate, as smaller nodules scattered throughout the wall or as broad areas of granulomatous tissue which invades the wall widely and diffusely.

There are a number of articles on the surgical aspects of lymphogranuloma of the gastro-intestinal tract, mostly involving the reaction of localized foci (Steindl; Ringdal; Ogloblina; Sussig). Sussig reported 3 cases, and stated that the disease rarely occurs in this tract.

Primary isolated lymphogranuloma of the gastro-intestinal tract is rare, but evidently occurs. The case of Goedel seems to prove this. The condition was diagnosed clinically as appendicitis, and the patient was operated on; part of the ileum, cecum and mesentery were removed, and on microscopic examination showed lymphogranuloma. The patient

died of peritonitis after four days, and autopsy showed no evidence of lymphogranuloma in any other organ than the ileocecal valve. Howell described a case involving the retroperitoneal glands in which the course closely simulated that of acute appendicitis and the patient was operated on. Singer cited the first case of primary isolated lymphogranuloma of the stomach reported in this country. Autopsy showed no other involvement. DeJong's case involved a loop of small intestine, but he did not include a report of the autopsy. Drope's case involved the stomach, with limitation to the gastro-intestinal tract and mesentery. Minot and Isaacs, reporting a series of 477 cases, chiefly of abdominal Hodgkin's disease and lymphoblastoma, stated that "Hodgkin's disease rarely causes large or multiple primary lesions of the gastro-intestinal tract while lymphosarcoma and pseudoleukemia often do so." Ikeda considered Hodgkin's disease of the gastro-intestinal tract in an article on lymphatic leukemia and included references to the literature. Wahl, Chand, Grevillius and Delanne and Lepage reported cases. Lang believed that lymphogranuloma of the gastro-intestinal tract probably started in the connective tissue of the mucosa and submucosa. References to the German literature were given. Wells and Maver, in 1904, collected the first cases of pseudoleukemia gastro-intestinalis. Lignac found a lymphogranulomatous ulcer of the lower end of the esophagus, without the symptom of dysphagia during the life of the patient.

Bone.—Opinion as to involvement of the bones varies widely. The reason may well be ascribed to the unequal determinative values conveyed by gross and microscopic examination of tissues and the inadequate diagnostic data furnished by roentgenograms. Reports based on roentgenographic findings are numerous, but to make a statistical study of the frequency of involvement of the bones on the basis of these reports alone would lead to considerable error. Tetzner found lesions of the bones in 9 of 10 cases in which autopsy was performed, and furthermore showed that certain vertebral lesions found at autopsy could not be demonstrated by roentgen examination, even when sagittal sections of the bones were made. Structural changes in the bones are of course demonstrated by roentgen examination, but the osseous lesions of lymphogranuloma are frequently not accompanied by such gross alterations. Symmers stated his belief that the marrow is always involved, but only thorough gross and microscopic examinations of the bones in numerous cases can decide that important point.

Ziegler believed that bone was involved in many cases, some of which showed very early osseous lesions. Blount's case illustrates such early involvement, the lesions of the bones preceding the lymphadenopathy by two years. Hamar's findings were similar.

Primary involvement of bone was reported by Montgomery. He stated that in such cases the disease may closely simulate bone tumor

or osteomyelitis and that the diagnosis rests finally on roentgen examination of the entire skeleton, with biopsies of bone to settle the question. Krumbhaar's unusual case was limited to the spleen and the bone marrow, the histologic picture of the marrow of the femur suggesting that the disease was primary in that site.

Arnell held that marked eosinophilia in lymph nodes points to an essential irritation and involvement of the marrow and that careful examination of the skeleton should be made. Stewart's observation that eosinophilia (in the blood) in a majority of cases may be considered as a specific reaction of the marrow in lymphogranuloma may be used in support of Arnell's contention. There has been frequent mention of Symmers' belief that the marrow is always concerned in this disease, and that the eosinophils in the affected nodes are derived from the blood, originating in the bone marrow.

Cases of general interest may be found in the papers of Saupe; Belot, Nahan and Kimpel; Baldridge and Awe, and Dresser and Krenser. Tetzner reviewed the literature and reported 10 new cases (with autopsies) in considerable detail, particularly with regard to involvement of the spine. Askanazy considered osseous lesions from the pathologic point of view.

Osteosclerosis (osteitis ossificans, endosteitis ossificans, condensing osteitis) in relation to Hodgkin's disease was discussed by Zypkin. He considered that the polymorphic stage of Hodgkin's disease is represented by an embryonal connective tissue from which bone can be formed, and he mentioned also the possibility of such formation of bone by an indirect route—through the commonly seen fibrotic stage which later becomes bone. He noted particularly the cases of Schwartz, Assmann, Baumgarten and Hammer. Osteosclerosis is much more frequent, although by no means common, in leukemias (Goodall; Weber; Sternberg; Fabian; Baumgarten; Zypkin; Kaufmann). Hulten recently cited a case of complete sclerosis of the second lumbar vertebra in lymphogranulomatosis.

Widespread lesions of bone were reported by Lockwood, Johnson and Narr. Matziani in a similar report stated his belief that such lesions are due to direct localization and not to extension from adjacent organs. Lesions produced by extension have been described in numerous instances and possibly form the larger part of the gross disease picture in bone. Involvement of the sternum, ribs or thoracic vertebrae is perhaps most frequent. Lortat-Jacob believed that the richness of the osseous marrow in the sternum is a reason for this localization. Düring and Cone cited such cases. While true infiltration of the spinal marrow is not frequently seen (Vasiliu and Goia; Robin), erosion and extension are common. One must not fail to appreciate how seldom the skeleton is examined microscopically, which may account for much

of the apparent rarity of infiltrative or metastatic lesions. Fraenkel's finding of granulomatous nodes, identical with those found in the spleen, in the general bone marrow should stimulate more careful search for such lesions. Sherman noted that metastases to bone react differently to x-rays than do lymph nodes, and particular caution was advised in the irradiation of vertebral lesions because of the possibility of producing local reactions in them, with consequent paraplegia.

Rolleston reported a rare finding—synovitis. The arthritis was usually transient and not well marked. Pfahler described involvement of the sacro-iliac joint.

In summing up the data on the lesions of the bones in Hodgkin's disease, the following points are stressed: (1) more careful and extensive roentgen examination of the entire skeleton, (2) biopsies on osseous lesions, (3) complete microscopic examination of numerous bones at autopsy whether they are grossly involved or not and (4) more careful description of the type of osseous lesion, and notation as to whether it is definitely traced to erosion, extension or metastasis.

Skin.—Involvement of the skin is present in a certain number of cases. It may be manifested merely by pruritus or by actual and more or less specific lesions. Ziegler's review showed the skin to be involved in 25 per cent of 70 cases of Hodgkin's disease. More recent figures are those of Cole (39 per cent of 33 cases) and of Barron (16 per cent of 24 cases). This is therefore a fairly common phase of the disease.

Pruritus may exist alone or with morphologic cutaneous lesions. Burnam reported it as present in 31.8 per cent of the series of 173 cases, and as being an initial symptom in 12 cases. He encountered it without definite lesions of the skin in 34 cases (19 per cent). Cole found it present in 8 of 33 cases (24 per cent). Barron, in a study of 24 cases, found the skin involved in 4; all of these showed pruritus at some time, and this symptom preceded the development of the lesions by several years. Ziegler's observations were similar. Desjardins and Ford reported pruritus as occurring much less frequently (in 9 per cent of 135 cases). Weber and Bode believed it to occur usually early in the course and seldom late. Favre and Colrat went so far as to designate the disease "*adénite prurigène éosinophile*" as a mark of their belief in the close association of pruritus and eosinophilia. Mariani corroborated this, but Cole refuted it, finding that the attacks of pruritus generally accompany a glandular flare-up. The cause of the pruritus is unknown, but various theories are offered. Paltauf held it to be caused by substances derived from the altered lymph nodes, and in this Shelmire and also Desjardins and Ford agreed with him. Other authors have referred the pruritus to a disturbance of the nervous system, such as irritation of the sympathetic system (Golay). Milian and Blum felt

that the pruritus may be due to radiculitis and be analogous to the pruritus of tabes dorsalis.

Ulceration is not common. Traut recorded the first case of spontaneous fistula over a mass of lymphogranulomatous tissue. Cole and also Langley reported cases of ulceration. Bine's patient showed an ulcer of the palate and a slough of a hemorrhoid without enlargement of the lymph nodes.

Primary Hodgkin's disease of the skin is described by a number of authors (Haxthausen; Kren; Saalfeld; Reisenberg and Kradlicky; Nanta and Chatellier).

Herpes is occasionally seen. Pancoast and Pendergrass reviewed the theories as to its causation—nerve irritation, pressure on a nerve by tumor tissue and toxic products producing a parenchymatous neuritis. They cited 4 cases. Mariani regarded all classic herpes as due to injury to the nervous system. Certainly it would seem that pressure on a nerve or on its spinal ganglion and also toxic products derived from the diseased tissue could cause this lesion. Lockwood, Johnson and Narr reported a case in which herpes zoster was the first symptom, and which later showed extensive destruction of the lumbar vertebrae.

Pigmentation occurs more rarely. Desjardins and Ford reported 2 cases. Laporte, Nieszkowski, Fowler, Bramwell and Symmers reported cases of pigmentation in association with masses of lymphogranulomatous tissue about the suprarenal glands. Rolleston believed pigmentation to be due to irritation of the sympathetic nervous system rather than to involvement of the suprarenals. Symmers reported a case of acanthosis nigricans with invasion of the celiac plexus and without involvement of the suprarenals.

The name "chancre lymphogranulomateux" was used by Nanta and Chatellier to designate an initial nodule which some believe places the disease in the same group as syphilis, tuberculosis and sporotrichosis. The similarity of this form to mycosis *d'emblée* is marked. Sharlit reported a case in which the surface lesions were limited to the oral and genital mucosa.

It is generally agreed that lymphogranuloma may occur in the skin in two forms—either with the specific histologic structure, which was first described by Grosz, or without this specific structure. In the latter form it may manifest itself by pruritus, pigmentation, edema, a prurigo-like exanthem, petechiae, bullae or urticarial lesions. Wise, and Jones and Alden described cases of generalized lymphogranulomatosis of the skin. Howard Fox and Cole reviewed the general aspects, as has Shelmire more recently. Miller, MacCormac, Arzt, McCarthy, Rulison and Keim have contributed articles of general dermatologic interest. McCarthy included the histologic aspects in his recent work on the histologic changes in the skin.

Genitalia (Female).—Gemmell described 17 cases in females in which it was possible to obtain a menstrual history. In 14 there was oligomenorrhea, in 3 menstruation was normal, and in 10 the patient was pregnant. In 25 of 57 cases the disease began during periods of amenorrhea. He considered the possibility of ovarian hypofunction. Winkelbauer and Priesel's case of possible placental or hereditary transmission is remarkable; the disease was present in both the mother and a newly born child. Minot and Isaacs noted the frequency of menstrual disorders but did not feel that the occurrence of such disorders in association with lymphoblastoma must be attributed to disease within the abdomen. Barron described a completely normal pregnancy occurring six years after the development of enlarged nodes.

Involvement of the uterus is rare; to my knowledge but 2 cases have been reported (Jessup; Lewinski). Ovarian involvement was described by Wallthard and by Mousson. Szenes' case presented involvement of the internal genitalia and bladder, a condition which was unusually refractory to treatment.

Nervous System.—The first to describe involvement of the nervous system was the pioneer Murchison, in 1869, who also first described the type of fever frequently associated with Hodgkin's disease. Since his time, a limited number of reports have appeared dealing with lymphogranuloma of the nervous system, most of them from clinical sources. Such involvement has generally been considered rare, or at least uncommon. Ginsburg, in an analysis of 35 consecutive cases, was able to find definite evidence of involvement of the nervous system in 10 (27.7 per cent), which shows it to be a rather common phase of the disease. In the majority of cases the visceral lesions overshadow those of the nervous system, but occasionally the reverse may obtain (Ginsburg; Paullin).

The underlying pathologic process has usually been a tumor-like growth with compression of any compressible tissue within reach. It is to this phenomenon that most, but not all, of the paraplegias in lymphogranulomatosis are traced, the spinal cord, and rarely the brain, being so situated that any encroachment on the limited confines of the vertebral canal or cranium is certain to produce pressure on the cord or brain. Filling in of, or extension through, the intervertebral foramina, periosteal thickenings, erosions of vertebral bodies and infiltrations of the spinal meninges, either arising *in situ* or penetrating from an extra-vertebral initial source, are the most commonly found lesions (Paullin). The effects are almost always rather slow and progressive, but may be acute, even resulting in sudden death, as in MacCallum's case, in which there was erosion of the odontoid process with spontaneous fracture. Paullin's case of sudden death, with marked cerebral crisis, is unique, as no morphologic cause could be found. The effects may also be transi-

tory, as seen by the clearing up of a transverse myelitis in Simmons and Benet's case and in Forrest's case. Roentgen treatment will produce alleviation of such manifestations and must be considered (Blakeslee). Extremely rarely the point of attack may be the brain, as in Burnam's case. Fraenkel, East and Lightwood, Poynton and Harris, Paullin, Mueller, Blakeslee, Hale White, Weber, Belot, Simmons and Benet, and Rolleston have contributed case reports and discussions illustrating the mechanism and effects of pressure. So far, I have found but a single case of actual metastatic tumor in the parenchyma of either the brain or the cord (Power and Hala).

In some cases, however, the neurologic disturbances cannot be traced to the effects of compression. Allan and Blacklock cited a well defined case of Hodgkin's disease with autopsy in which the cerebral nervous system showed purulent meningitis (bacterial) of the brain and cord, with myelitis below the middorsal segments. Weber stated with regard to symptoms of involvement of the cord that "in by no means all the cases were these tumor-like growths affecting the vertebral column within the vertebral canal." He held that some of these lesions are found to be syringomyelia, pachymeningitis interna, tuberculosis associated with lymphogranuloma, or myelitis of the cord itself.

Forrest's case showed no lymphogranulomatous lesions of the vertebrae, canal or meninges, but there were slight degenerations of several tracts of the cord. He cited 4 other parallel cases. Shapiro contributed 2 cases, one of transverse degenerative myelomalacia and one of subacute posterolateral sclerosis. Burnam's series included a case with symptoms of meningitis. Johnston's case presented two separate neurologic processes—degeneration of spinal tracts due to anemia and intoxication and pressure atrophy due to perineural infiltration.

The cause of such lesions must, of course, vary in the different cases (Weber). Forrest offered as the theoretical explanation for the lesions in his case liberation of toxins, pressure by the pathologic tissue on vessels supplying the cord or general anemia; he felt that anemia was the most probable cause. One must not lose sight of the fact that aside from the possibility of pressure on blood vessels their walls may be invaded so as to produce local anemias. Shapiro's explanation for his case of myelomalacia is that it was produced by nonspecific proliferation of the arachnoid mesothelial cells in the "duraneural angle," which blocked the lymphatic drainage and led to lymph stasis. The possibility of this phenomenon is demonstrated by the excellent illustrations of Spielmeyer. Shapiro considered the formation of toxins as the cause of the lesions in his second case. Weber asked whether high voltage roentgen therapy could cause transverse degenerations of the cord leading to paraplegic effects. Rolleston considered the possibility of an arsenical neuritis being responsible for paraplegia in Carlill's case.

Reports of unusual neurologic manifestations are scattered throughout the literature. Baldridge and Awe cited a case in which Horner's syndrome was present, possibly due to paralysis of the cervical sympathetic system. MacNally mentioned the occurrence of irregularity of the pupils when the sympathetic nervous system was involved. Simmons and Benet listed 2 cases with exophthalmos. According to Paullin, nervous symptoms may precede all others.

The occurrence of herpes zoster is fairly common. Weber, in discussing Carslaw and Young's case, called attention to the possibility of the involvement of the posterior roots and ganglions by the abnormal tissue, stating that no cases of herpes zoster had been reported with such infiltrations, perhaps because the vertebral canal was not examined at autopsy. Pancoast and Pendergrass reviewed the theories as to the cause—irritation of a nerve, pressure on a nerve by tumor and toxic effects producing a parenchymatous neuritis. They stated that other malignant conditions also cause this lesion. Mariani regarded the various clinical forms of herpes as merely variations of a fundamental process of reaction, such as injury to the nervous system. He did not refer specifically to lymphogranuloma.

Pruritus as a neurologic symptom, according to Milian and Blum, is possibly due to radiculitis, being analogous to the pruritus of tabes dorsalis. Golay stated that it may be due to irritation of the sympathetic nervous system. Paltauf, Shelmire, and Desjardins and Ford interpreted pruritus as of toxic origin, usually caused by substances in the circulation derived from the diseased lymph nodes. The association of eosinophilia was greatly stressed by Favre and Colrat. Mariani also noted a close relationship. Cole, however, could not corroborate this, finding that the attacks of pruritus accompany a glandular flare-up.

Pain has generally been considered as absent in the enlarged nodes, but they may at times present this symptom. MacNally vividly described such cases; the pain occurs chiefly during periods of pyrexia, the nodes being hot, swollen, soft and tender; as lysis occurs, the condition recedes and the nodes become painless until the next period of pyrexia occurs. Pain is most commonly found in abdominal cases, in which it may be vague, moderate or intense, and either generalized over the abdomen or so localized as to simulate closely several conditions (perforation of an intestinal ulcer as in typhoid [McAlpin and Von Glahn], acute appendicitis [Howell], peritonitis [Whillington] and chronic appendicitis or cholecystitis). In a case of mine the abdominal pain was excruciating and almost continuous, morphine being used freely. Laparotomy was performed, and two large retroperitoneal masses were found in the region of the celiac plexus. High voltage roentgen therapy gave considerable relief. Fox and Farley mentioned the occurrence of paroxysmal pain in the lower part of the abdomen in cases of granuloma of

the abdomen. Cunningham, in reporting a series of 25 cases, called attention to pain as a reason for consulting the physician (pain alone in 4 instances and tumor and pain in 2). Desjardins and Ford found pain frequently. They described the symptom as of two types: (1) pain due to pressure phenomena and (2) intermittent pain occurring in bones and joints and present in the later stages, moving from place to place, and examination showing nothing to account for it. Isaac mentioned backache as a symptom. Ducamp and Rimbaud described pain due to a mediastinal mass; it was relieved by irradiation.

Grabner cited a case of lymphogranuloma with paroxysmal tachycardia in which fatty degeneration of the vagus nerves was found, due to pressure by a mediastinal mass. This is exceptional, as most cases of paroxysmal tachycardia have not been shown to be due to stimulation of the extrinsic cardiac nerves. MacNalty described cardiac irregularity resulting from pressure of enlarged cervical nodes upon the vagus.

Weil (1931) collected reports of 43 cases of involvement of the spinal cord from the literature, and added a report of 3 new cases, with operative findings and autopsy observations. The involvement of the cord was cervical in 16 per cent, thoracic in 80 per cent, and lumbosacral in 4 per cent.

ETIOLOGY

The etiology of lymphogranulomatosis constitutes a most difficult phase of the subject, for it is closely linked with speculation and theory concerning the true nature of the disease. Stewart and Dobson grouped the different views under the following headings: (1) an atypical form of tuberculosis; (2) a specific infection by a diphtheroid bacillus; (3) a granuloma of unknown etiology; (4) a neoplastic disease. These several categories, while comprehensive, do not sufficiently bring out all of the possibilities. An attempt will therefore be made to summarize briefly the reported evidence.

As to lymphogranuloma being an atypical form of tuberculosis, the question will be discussed under a separate heading.

The second point of view, that lymphogranuloma is due to infection by a diphtheroid bacillus, is still maintained by some authors and contradicted by others. Bunting and Yates described lesions produced in monkeys by injection of the bacillus which they believed to be the etiologic agent, but with the exception of certain reactions resembling Hodgkin's disease the results did not establish the theory. Twort, in a long series of experiments, could not confirm it. The diphtheroid organisms have been held to be merely air-borne laboratory contaminants which are not found when strict sepsis is maintained in laboratory procedures.

The idea that lymphogranuloma is a granuloma of unknown etiology has the most adherents. Twort advanced a theory involving a filtrable virus on the basis of a study of allied diseases unquestionably caused by a virus, such as leukemia of fowls and pernicious anemia of horses. Favre and Croizat were of the opinion that the specific histologic picture suggested the local reaction to a virus which tended to display unequal activity in different nodes or tissues.

Barron advanced the opinion that lymphogranuloma might be due to an animal parasite and suggested that the inclusion bodies of Kuczynski and Hauck might be such parasites or the cellular reaction to them. He further stated that certain features of lymphogranuloma, such as the peculiar relapsing type of fever, the eosinophilia and the nontransmissibility to animals, militate against vegetable parasites as causative agents. Kofoed's theory, proposing an ameba, could not be confirmed by Schreiner and Mattick, or by Twort.

Several observers have reported the presence of fungus-like bodies. Kuczynski and Hauck believed that the etiologic agent is a type of higher bacteria midway between *Bacillus tuberculosis* and *Actinomyces*. They have described inclusion bodies in the cells of the lesions. Merk reported a thallophyte as the etiologic agent. Haythorn reported the finding of a monilia, which he believed to be a secondary invader. Twort, in his most recent and extensive report, stated that he could not find any evidence of fungi.

Busni's organism is described in the section on bacteriology; the claims are broad, and no corroboration has appeared. Grumbach's organism has been claimed to be etiologic.

Bunting and Yates suggested that staphylococci, which they found in almost all cases, play the part of secondary infectious agents, and that secondary infection plays a part in the development of the disease.

Piney stated his views as to lymphogranuloma being a reticulo-endotheliosis, and Brandt agreed with him. "Lymphogranulomatous tissue is a mere mark of a severe injury of the reticuloendothelials through different causes and is not a disease of a specific sort." This idea is a distinct departure, and might be invoked to explain the occasional "atypical" cases of lymphogranuloma, so confusing to the microscopist.

The theory that lymphogranuloma is a true neoplasm has been advanced, especially in the more recent publications. Perhaps the oldest concept of neoplastic origin is that involving the lymphoblast (Mallory, Warthin, and others), which assigns Hodgkin's disease a place in the category of lymphoblastomas under the designation "lymphoblastoma of the Hodgkin's type," or that of "scirrhus, or sclerosing, lymphoblastoma." This terminology would indicate a relationship with other lymphoblastic diseases, such as lymphosarcoma and

lymphoid leukemia, a part of the subject which is reviewed in the section on classification and relationships. The claim has been definitely made that the lymphoblast, as typified by the pale cells of the so-called germinal centers, is the offending element, the fibrosis and the polymorphic histologic picture being a reaction to this stimulant or to other secondary stimuli (Tsunoda).

Symmers gave his opinion that the disease is primarily granulomatous but that it may undergo malignant transformation, and that it has its origin in the bone marrow. Dietrich described it as a granulomatous lymphosarcoma. Scala believed it to be an intermediate form between a neoplasm and a granuloma, a theory also held by others. He stated that while epithelioid cells and histiocytes suggest granuloma, the Sternberg giant cells with their active reproductive processes are analogous to those of the hemolymphopoietic system and to those of the blastomas; the stroma is developed in symbiosis with the parenchyma.

Medlar recently suggested another cellular origin, namely, from the progenitors of the megakaryocytes, and placed the primary lesion in the bone marrow, the lesions outside of the marrow being metastatic tumors. He emphasized what he regarded as the predominant phase of lymphogranuloma by designating the disease as "megakaryoblastoma." This would suggest a close genetic relationship with the myeloid leukemias and the erythroblastic dyscrasias. His views, especially those concerning the derivation of cell types, are original.

Twort, in a large series of cases, tried many methods of investigation (direct examination for vegetable and animal parasites, examination of apparently healthy organs for protozoa, injection of lymphogranuloma filtrates and of bacteria into animals, sensitization experiments, attempts to produce specific antibodies in animals, examination of blood, other body fluids and excreta of both patients and inoculated animals, bacteriologic investigations, etc.). He concluded that "so invariably did the different experimental procedures we adopted lead to nothing that one might be dealing with a new growth instead of what is generally accepted to be granuloma."

I wish here to call attention to the relation of age and sex to the incidence and progress of the disease. Bunting suggested the importance of this relationship, and Gemmell stressed the probable effects of ovarian hormones. From a study of the age of the patients in a large number of cases taken from the literature and from my own experience, a striking curve may be drawn. The curve shows an initial rise up to the age of 5 or 6 years, with a gradual decrease as the age of puberty is reached; between the ages of 11 and 15 years the cases are much less numerous; this period is followed by a sharp elevation of

the curve. This, together with the established preponderance of male over female patients, seems to link the disease with growth and sex development or function. I feel that these facts concerning age and sex must be considered as strongly entering into and forming a part of the problem of etiology.

TRANSMISSION

Transmission of Hodgkin's disease has never been accomplished by any method. Lesions that are practically indistinguishable from the classic picture have been produced in animals; yet the progressive development characteristic of the disease is always lacking. The clinical picture with inevitable termination in death has not been produced. Attempts at transmission may be outlined as follows: (1) injection of emulsions of lymph nodes or other tissue; (2) surgical implantation of nodes; (3) injection of various bacteria and fungi recovered from the patient; (4) injection of the patient's or the animal's blood or urine. The results obtained have been far from satisfactory, regardless of the method.

Little is to be gained in a review of this kind by a lengthy citation of inoculation experiments. The work of Bunting, Tyzzer, Cunningham and McAlpin, de Leon and Reyes, and Longcope on monkeys and apes has uniformly given negative results. Stewart and Dobson, and especially Twort, made extensive investigations, with negative results. Wachsmuth described the changes occurring in transplanted normal lymph nodes, noting early central necrosis, followed by cellular infiltration and proliferation of connective tissue, with complete disappearance of the architecture. As these are some of the changes usually described in connection with the implantation of Hodgkin's nodes they carry considerable significance.

Tyzzer implanted a piece of a node under the patient's own skin. It remained for ten days and then entirely disappeared. Simmons and Benet commented on this, suggesting that "a fragment of sarcoma or carcinoma treated in a like manner would probably have grown. This fact is rather against the tumor theory." More observations are necessary.

Twort produced local inflammatory nodules, believed to be due to toxins present in the injected tissues. Filtered emulsions of these cells led to no nodular formations, and incubation of the tissue with certain serums rendered them innocuous. Coyon and Brun asserted that they transmitted a "virus" by way of the blood stream which produced the histologic features of the disease in a guinea-pig. Tixier, in discussing this, suggested that great prudence must be exercised in the interpretation of such lesions, as they may be only a special form of tuberculosis. Loeper and Lemaire injected the blood and urine of

patients into guinea-pigs and concluded that they are specifically noxious to these animals. The lesions produced, while not the specific lesions of lymphogranuloma, could not be produced by the blood and urine of normal human beings. Sacquépée, Liegeois and Codvelle obtained histologic appearances resembling Hodgkin's disease in guinea-pigs by the injection of human material.

Numerous attempts have been made to transmit the disease by the injection of bacteria and fungi recovered from patients by culture. Here also the results may be considered as inconclusive. Grumbach obtained interstitial pneumonitis with suggestive pathologic features in guinea-pigs by the injection of an organism isolated from the blood during an acute phase; he also reported lesions resembling those of Hodgkin's disease following the injection of a peculiar diphtheroid bacillus. Busny claimed to have produced lesions similar to those of lymphogranuloma by the injection of peculiar acid-fast and coccoid organisms. These organisms could be found in all the tissues of the patient, and Busny believed that lymphogranuloma might be established as a generalized bacteremic infection. A series of passages of diseased splenic tissue appeared to increase the virulence in animals, the organisms mentioned being recovered in each case.

Histologic pictures which at times rather closely resemble that of lymphogranuloma may be produced by benzene, tar, actinomycetes, tuberculosis and syphilis, according to Brandt. Mueller cited the production of a polymorphocellular sarcoma by Kopsch, who fed the larvae *Rhabditis pellio* to frogs.

Vasiliu and Irimoin made numerous attempts to transmit the disease, and Sternberg mentioned that Vasiliu had obtained results that seemed to support strongly his belief in the tuberculous nature of lymphogranuloma. Medlar called attention to the close resemblance between the lesions of lymphogranuloma and those of avian tuberculosis. Schütt also noted the resemblance to Hodgkin's disease of tuberculosis occurring in guinea-pigs that had been inoculated with lymphogranulomatous material.

Concerning the congenital or hereditary transmission of the disease in man, the evidence is meager. Priesel and Winkelbauer cited one of the most remarkable cases in the history of the disease. Two weeks before the end of a normal pregnancy a diagnosis of lymphogranuloma was made by biopsy. The child was delivered normally, but it soon became ill, presenting enlarged nodes which were diagnosed as lymphogranuloma microscopically. It died shortly thereafter. Arkin reported 3 cases in a family, occurring in the father, a son and a nephew. Several cases have been reported in which women with the disease were delivered of perfectly normal children. Gemmell made an

extensive study of pregnancy in Hodgkin's disease; and in 57 cases he mentioned no instance of transmission to the offspring. Allan and Blacklock cited the cases of 2 brothers with Hodgkin's disease.

BACTERIOLOGY

The bacteriology of Hodgkin's disease presents confusing and variegated findings, none of them generally accepted as etiologic.

Dreschfeld, in 1892, was the first to describe a bacillus in connection with the disease. Delbet, in 1895, reported another bacillus. Bramwell may also be cited as an early worker in the field. Abram, in 1898, was one of the first to recover an organism from the blood—a gram-negative micrococcus. He cited the early literature: Klebs (a bacillus); Weigert (acid-fast bacilli in the nodes); Kelsch and Vaillard (a coccoid bacillus in a leukemia); Traversa (streptococci in the blood); Grossi (streptococci in the blood); Lannois and Groux (*Staphylococcus aureus*). Abram believed that the micrococcus was a secondary invader and that the enlarged nodes decreased in size during the period of secondary infection, to enlarge again when the organisms disappeared from the blood.

Various types of cocci have been cultivated. Rosenow stated that "cocci predominate in the more recently enlarged glands." Fox and also Schütt found a large diplococcus. Cordier, Levy and Nové-Tosserand obtained an enterococcus from the blood. Streptococci were reported by Mathes and also by Miller, who interpreted his finding as a preagonal invasion. Cunningham stated that "staphylococci and streptococci may give rise to a picture simulating Hodgkin's disease histologically, either by direct infection or as an irritative reaction." Litterer, finding *Staphylococcus albus* in 4 cases, believed that it had something to do with the exacerbations. Haythorn, Robinson and Johnson described an unusual reaction produced in animals by the injection of a monilia recovered from a patient. They described the condition as Hodgkin's disease with secondary infection by the monilia. Twort found curious bodies resembling the spores of a fungus (*Alternaria*?) in 5 per cent of his cases; he found streptococci and diphtheroid and tubercle bacilli occasionally. Grumbach did considerable work on a bacillus resembling *Corynebacterium diphtheriae* and differing from the various pseudodiphtheria bacilli. He made no claim as to etiology, but stated that the bacterium on inoculation into animals produced lesions almost like those of Hodgkin's disease. The organism appeared coccoid at first, then like *C. diphtheriae*, and then irregular.

Busni described a curious organism which began as an acid-fast rod and changed to a coccus. The same organism was found in cases of mycosis fungoides. Grandclaude, Lesbire and Foulon, by delayed

anaerobic cultures of lymph nodes of patients with the disease obtained organisms similar to Busni's (bacillary and coccus forms). They placed them in the group studied by Haudroy and by Haudroy and Lesbre, believing that they played the part of biohormones in abnormal cell proliferation, and they did not assign them an etiologic rôle.

Blood cultures have often given negative results (Cunningham; Barron; MacNalty). Splenic punctures gave negative results on two occasions (MacNalty). Direct examination of blood films for parasites has never shown any (MacNalty, and others). Twort examined the feces, finding no Protozoa which could be associated with the disease. He also was unable to demonstrate toxins or bacteriophages.

In my own experience diphtheroid bacilli and cocci have been found. Recently a peculiar streptococcus was obtained after one month's incubation on Kendall's new medium. Diphtheroid bacilli have often been recovered from excised nodes. The rôles of various diphtheroid bacilli, especially that of *Corynebacterium hodgkini* (de Negri and Mieremet; Bunting), are well outlined in Simonds' review. While final decision is reserved, it is generally held that these organisms are not etiologic. Kusunoki held the opinion that they are more abundant in cases in which the growth of the peculiar large cells is prominent and in which giant cells are numerous, and less numerous in markedly fibrotic nodes. He gave a considerable bibliography. Other papers on the subject have been published by Rhea and Falconer, Simon and Judd, Steel, Verploegh, Ayrosa, Hirschfeld, Rosenfeld, Dietrich, Simonds, Luce, Fox, Cunningham, Henrici, Mellon, Bunting, and de Negri and Mieremet.

Ameba.—Kofoid's theory that an ameba is etiologically related to Hodgkin's disease has neither been generally discussed nor accepted. Barron, however, expressed his belief in the possibility of the etiologic agent being an animal parasite and cited reasons therefore. He stated that while Kuczynski and Hauck's theory (that the disease is an infection by a fungus or that the inclusion bodies in the Sternberg cell are plant or higher bacterial forms) is questionable, "the indefinite pleomorphic cellular inclusions which they describe correspond much more closely to animal parasites or the cellular reactions to animal parasites," and that such animal parasites could conceivably fulfil all the requirements of an etiologic factor in Hodgkin's disease. Coffen, in discussing Barron's paper, supported the idea of an animal parasite. Both of these authors argued for this theory on the following grounds: (1) Practically all known chronic relapsing fevers are caused by animal parasites (malaria, trypanosomiasis, relapsing fever, kala-azar, etc.); (2) eosinophilia is commonly associated with diseases caused by animal parasites (trichiniasis, filariasis, trypanosomiasis and helmin-

thiasis); (3) tuberculosis and other known bacterial infections never produce any definite eosinophilia, unless by allergic reactions, as in bronchial asthma, and (4) the fact that Hodgkin's disease is not transmissible to animals is more in keeping with the possibility that it is caused by an animal parasite.

In summary, it may be said that, by the methods of the present day, no organism or parasite can be shown to produce the disease.

(To be Concluded)

Notes and News

University News, Promotions, Resignations, Appointments, etc.—R. A. Webb has been appointed professor of pathology in the school of medicine for women at the University of London.

As previously noted, a department of forensic medicine has been established in the University and Bellevue Hospital Medical College, New York, with the following staff: Charles Norris, professor of forensic medicine; Alexander Gettler, professor of toxicology; Douglas Symmers, professor of gross pathology; Harrison S. Martland, associate professor of forensic medicine; Thomas A. Gonzales, assistant professor of forensic medicine, and Armin V. St. George, assistant professor of gross pathology. Six lectures dealing with the relationship between the physician and the medical examiner's office and other medicolegal topics will be given all fourth year students. The main instruction in forensic medicine, however, will be in the form of elective courses and in graduate work. The department is linked with the medical examiner offices of the City of New York and of Essex County, N. J.

Carl F. Kleine has succeeded Fred Neufeldt as director of the Robert Koch Institute for Infectious Diseases in Berlin.

Herbert U. Williams, professor of pathology in the University of Buffalo, has been granted leave of absence for travel until the middle of March, 1934. During his absence the work in pathology will be directed by a committee from the faculty.

Committee for Survey of Research on the Gonococcus and Gonococcal Infections.—This committee has been formed by the Division of Medical Sciences of the National Research Council in cooperation with the American Social Hygiene Association. Its purpose is to collect, analyze and collate the facts already established and the efforts now in progress to add to knowledge of the gonococcus and gonococcal infections, especially as regards bacteriology, pathology, immunity, the mechanism of infection and some of the forms of therapy. Attention will be concentrated chiefly on work done in the United States. At the close of the preliminary survey the committee, with the assistance of a conference of experts, will compile a report with the object of stimulating interest in the study of the gonococcus, of providing a point of departure and of suggesting promising leads for further investigation. The survey will cover the literature, but it is hoped that unpublished work and studies which were incomplete or the results of which were inconclusive may also be included. Dr. Stanhope Bayne-Jones, chairman, earnestly invites the cooperation of workers interested in this field. Headquarters have been established at Room 1101, 450 Seventh Avenue, New York, where communications and reprints will be welcomed.

CORRECTION

In the abstract of an article by Drs. David P. Seecof, Charles R. Linegar and Victor C. Myers, entitled, "The Difference in the Creatine Concentration of the Left and Right Ventricular Muscles of the Heart," which appeared as part of the proceedings of the American Society for Experimental Pathology in the August issue (*ARCH. PATH.* 16:308, 1933), an error occurred in the fifth and sixth lines of the second paragraph. The statement "per hundred cubic centimeters of blood" should have read "per hundred grams of muscle."

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

SPLENECTOMY IN BILE FISTULA DOGS (BILE PIGMENT OVERPRODUCTION, ANEMIA AND INTOXICATION). F. B. QUEEN, W. B. HAWKINS and G. H. WHIPPLE, *J. Exper. Med.* **57**:399, 1933.

A splenectomized dog can be kept anemic for months or years in perfectly good condition. A dog with a renal biliary fistula, on a suitable diet, can be kept in perfect health and activity, with normal weight, for years. When splenectomy and a biliary fistula are combined, one invariably observes, after a latent period, a striking reaction, with an enormous overproduction of bile pigment, definite anemia and finally death from anemia or from hemorrhage in the tissues. The spleen is essential for life in an animal with a biliary fistula, and this suggests an association of the spleen with the internal metabolism of the body. The spleen and bile together are essential for the normal metabolism of pigment. It is thought that the bile salts play some obscure rôle in this reaction. It is difficult to explain the excess of bile pigment as coming from hemoglobin built up from the usual diet factors which, in our experiments, were well standardized. It is suggested that the body can synthesize the pyrrol aggregate (four pyrrol rings). There is some evidence that the liver can build up bile pigment directly from "building stones." It seems necessary to postulate one or the other mechanism, and they do not seem unlike in the final analysis, as both bile pigment and the pyrrol aggregate contain four pyrrol rings. Possibly both reactions may take place under these conditions.

AUTHORS' SUMMARY.

CELLULAR MECHANISMS OF RENAL SECRETION. J. R. OLIVER and E. M. LUND, *J. Exper. Med.* **57**:435 and 459, 1933.

The secretion of neutral red reproduces the variations which are observed in the mitochondrial apparatus of the renal tubule cells of animals living under natural conditions. The tubular absorptive processes concerned with water, salts and sugars do not produce these effects. The changes in the mitochondria consist of alterations in both the structure and the constituents. These have been shown to be not merely phenomena concomitant with secretion, but a determining factor in one part of this process, namely, in the concentration of the dye within the cell.

The elimination of neutral red by the renal epithelium is a composite process, consisting of direct and indirect secretion. The mechanism controlling direct secretion is concerned with the permeability of the two cellular membranes. These membranes may be affected independently in the direction of either an increased or a decreased permeability, with a corresponding increase or decrease in the elimination of the dye. The mechanism controlling indirect secretion is concerned with the mitochondrial apparatus of the cell. By means of change in form and constituent substance, the dye is concentrated within the cell and is slowly eliminated. Direct secretion, depending on the condition of sensitive membranes, is easily disturbed. Such disturbances account for the wide variations in the elimination of dye observed in the functioning of abnormal kidneys. Indirect secretion, depending on the simpler factor of the solubility of the dye in the protoplasmic constituents, continues even when the cells are severely damaged.

AUTHORS' SUMMARIES.

EPITHELIAL REPAIR IN RECOVERY FROM VITAMIN A DEFICIENCY. S. B. WOLBACH and P. R. HOWE, *J. Exper. Med.* **57**:511, 1933.

In vitamin A deficiency, the stratified keratinizing replacement epithelium is morphologically identical in all locations. All the cells of the lowermost layer of

the replacement epithelium have proliferative power, as in the stratum germinativum of the epidermis. In recovery, in spite of the complete morphologic masking, the epithelium in each region returns to its normal type. The important histologic features of repair involve removal of the layers of cells irreversibly differentiated toward keratinization and direct differentiation of the stratum germinativum toward the normal type. These take place simultaneously. The histologic sequences observed in the removal of cells above the stratum germinativum indicate that autolysis, as shown by vacuolar degeneration, and heterolysis, as shown by leukocytic infiltration, are involved. The cycle of vitamin A deficiency, metaplasia and recovery affords an experimental method available for the correlation of nuclear chromatin and types of cytoplasmic activities.

AUTHORS' SUMMARY.

THE RELATION OF MANGANESE TO LIVER CHANGES. P. K. RAO, Beitr. z. path. Anat. u. z. allg. Path. **87**:599, 1931.

Acute manganese poisoning in rabbits produced severely necrobiotic processes in the periphery of the lobules of the liver, and, in general, death supervened before reparative proliferation occurred. Cirrhosis could not be produced. Chronic continuous manganese poisoning caused monolobular cirrhosis, with cell proliferation and an interstitial increase of the collagenic and argentophil fibers in the periportal area. Chronic intermittent manganese poisoning produced either no effect or a very minor degree of cirrhosis.

W. S. BOIKAN.

Pathologic Anatomy

A STUDY OF THE HEART IN HYPERTHYROIDISM. GEOFFREY RAKE and DONALD MCEACHERN, Am. Heart J. **8**:19, 1932.

Both the results of autopsy and the experimental material point to the fact that hyperthyroidism by itself produces no specific lesions in the myocardium. It is conceivable that the damage produced by physiologic wear and tear or by an associated infection or disease tends to be more accentuated in a person with hyperthyroidism than in a normal one. It is difficult to be certain whether or not the injury in cases such as those described by Fahr, Goodpasture and Lewis, and two in the present series, in which profound damage is present without any coexisting complicating disease, represents the effects of a toxin derived from the thyroid gland and circulating in the blood. The evidence points against the occurrence of a specific causal toxin producing specific myocardial lesions. It is felt that in the past too much emphasis has been laid on the morphologic changes in the myocardium, with consequent neglect of important alterations in the metabolism and function of the muscle fibers. In this connection attention may be drawn to the recent work on the glycogen content of voluntary and cardiac muscle in hyperthyroidism. It has been shown that in the experimentally produced disease no glycogen can be found in the myocardium microscopically or by chemical analysis. As a result of this, rigor mortis sets in immediately, a fact which the authors can abundantly confirm from their experimental experience. It is well known that the withdrawal of glycogen from cells normally well supplied with it renders them more liable to injury, to which they react by diminished function, structural change and death. This problem has been thoroughly examined in the case of the liver, and one may well believe that similar reasoning can be applied to the myocardium. It seems more than probable that a close examination of this physiologic problem and others will bring one nearer to an understanding of the cardiac abnormalities in hyperthyroidism.

AUTHORS' SUMMARY.

THE HEART IN EXPERIMENTAL HYPERTHYROIDISM. FRANK R. MENNE, ROGER H. KEANE, ROBERT T. HENRY and NOBLE W. JONES, Am. Heart J. **8**:75, 1932.

Hyperthyroidism produced experimentally in rabbits for twenty-three days by means of (1) thyroxine, (2) thyroid and (3) desiccated human thyroid (from

patients having exophthalmic goiter) resulted in the following changes in the hearts: parenchymatous and fatty degeneration, histiocytic invasion, fraying of the muscle bundles and early fibrosis. Similar changes may be produced by cardiac overwork irrespective of the presence of an excess of thyroxine in the circulating blood, as is indicated by the results obtained on cutting depressor nerves and denuding the carotid sinuses of their investments in order to allow the heart to operate uncontrolled. There is no evidence in the literature to disprove the fact that a heart which is induced to work more rapidly, with an increased output in the presence of increased pressure and metabolism (as is true in hyperthyroidism), may not exhaust its nutrition and respond with morbid anatomic changes that may be erroneously ascribed to the pernicious influence of thyroxine on the myocardium.

AUTHORS' SUMMARY.

CONGESTIVE HEART FAILURE AND HYPERTROPHY IN HYPERTHYROIDISM. E. J. KEPLER and A. R. BARNES, *Am. Heart J.* 8:102, 1932.

In 27 of 178 fatal cases of hyperthyroidism severe congestive failure of the heart occurred. Eighteen of these cases (67 per cent) were associated with coronary sclerosis, hypertension, acute or chronic pericarditis, rheumatic endocarditis or syphilis. In the remaining cases no cause for the congestive failure other than hyperthyroidism could be found.

AUTHORS' SUMMARY.

SPONTANEOUS RUPTURE OF THE AORTA. OSKAR KLOTZ and WINIFRED SIMPSON, *Am. J. M. Sc.* 184:455, 1932.

The authors analyze five cases of so-called spontaneous nonsyphilitic rupture of the aorta. The underlying process consisted of a peculiar noninflammatory degeneration of the media, affecting the muscle and elastic fibers and similar to the lesions which precede the development of dissecting aneurysms. This degenerative process in the aorta seems to have been due to a variety of factors, viz., bacterial toxins, exogenous poisons, such as nicotine and epinephrine, toxic products of deranged nitrogen and glycogen metabolism and possibly certain dietary deficiencies. In one case there was thrombosis of the nutrient arteries of the aortic wall. The peculiar medial degeneration without spontaneous rupture or dissecting aneurysm is found with increasing frequency with advancing age, either as a diffuse process or in patchy distribution throughout the aorta.

SANDER COHEN.

MELANOMA STUDIES: I. THE DOPA REACTION IN GENERAL PATHOLOGY. GEORGE F. LAIDLAW, *Am. J. Path.* 8:477, 1932.

The dioxyphenylalanine reaction was introduced by Bloch, the dermatologist of Zurich. Dioxyphenylalanine is a phenol which oxidizes readily to melanin. Melanoblasts and myelogenous leukocytes hasten the oxidation and stain black from the accumulation of dioxyphenylalanine melanin in or on them. The blackening of the cell constitutes a positive reaction. Bloch holds that the conversion of dioxyphenylalanine to melanin is the work of a ferment of the reacting cell. He holds further that this oxydase is the natural melanin-producer of mammalian skin.

Laidlaw accepts Bloch's explanation as the best working hypothesis of the production of melanin, both normal and pathologic, in mammalian skin. He finds that the abundance of cells giving a positive reaction to dioxyphenylalanine is parallel with the activity of melanin production. For instance, if leukocytes are excepted, cells giving positive reactions are found only in tissues where melanin is being produced or where it can be produced under appropriate stimulation. When melanin is being formed in excess, as in Negro skin, in irradiated Caucasian skin, in pigmented moles and in the pigmentation of Recklinghausen's disease, the number of the positively reacting cells and the complexity of their dendrites are increased. When the power to form melanin is congenitally absent, as in the white skin of animals, or has been lost, as in vitiligo of Negro skin, no such cells are found. When the production of melanin is resumed, as in the repigmentation

of vitiligo or of scars, cells giving positive reactions always reappear before the production of melanin. These cells are found also in mucous membranes of ectodermal origin, such as the conjunctiva and the mucosae of the mouth, lips, gums, external genitals and anal canal, all frequent sites of melanin formation. An unexplained phenomenon is the constant occurrence of dioxyphenylalanine-positive cells without pigment formation in the acanthoses.

The melanin-bearing cells of the derma never react to dioxyphenylalanine. They contain no ferment and are thought to be phagocytes, not melanoblasts. The only exception is the pigmented cell, a true mesodermal melanoblast and the sole source of melanosarcoma of the skin.

The dioxyphenylalanine reaction has no relation to malignancy. The cells of ordinary sarcoma and carcinoma never give the reaction. In some carcinomas, a few cells that give a positive reaction are found scattered among the epithelial cells, but they are of no significance. In melanosis coli, the melanin-bearing cells give a negative reaction, confirming the orthodox opinion that these cells are phagocytes, not melanoblasts.

The author rejects the common opinion that mammalian melanoblasts are necessarily dendritic like those of amphibia and of reptiles. He shows that in normal mammalian skin, in pigmented moles and in malignant melanomas, the melanin-producing cells and phagocytes alike may assume any shape, round or cuboidal, without dendrites or highly dendritic. The shape of the cell has no relation to its power of producing melanin.

The author confirms Bloch's contention that the reaction to dioxyphenylalanine and the silver reaction of melanin-bearing cells are totally different. Silver blackens melanin wherever it is found, in both melanoblasts and phagocytes and in the interstitial tissue. Leukocytes being excepted, dioxyphenylalanine blackens only the melanoblasts and these only when they contain an active ferment. Pigmented moles and melanomas contain many tumor cells which do not react to dioxyphenylalanine. These are latent melanoblasts which may at any moment resume their melanin-producing function, in which event they will give a positive reaction.

The paper includes photomicrographs showing reactions to dioxyphenylalanine and a full bibliography. A résumé of the material on the reaction and on the technic was published in the *Anatomical Record* (53:399, 1932).

GEORGE F. LAIDLAW.

PRODUCTION OF NONFATAL VASCULAR SCLEROSIS IN RABBITS BY MEANS OF VIOSTEROL (IRRADIATED ERGOSTEROL). T. D. SPIES, Arch. Int. Med. 50:443, 1932.

In the experiments reported the administration of repeated, massive doses of viosterol produced severe and persistent sclerosis of the aorta and renal vessels. This phenomenon was associated with deposition of calcium within the parenchyma of the lungs and kidneys. It is worthy of emphasis that soon after the final dose of viosterol was administered all the animals regained their normal appetite and body weight. They continued to have normal renal function. At the termination of the experiment, they appeared in the best of health. In general, the vascular process was one of extensive sclerosis with hyalinization and calcification of the media. The pulmonary changes consisted of calcification of the trachea, the bronchial cartilages and, at times, the bronchial and alveolar epithelium. Deposits of calcium were absent in the pulmonary vessels. The renal arteries, arterioles, tubules and glomerular capsules were hyalinized and calcified. The lesions were slightly less prominent than those of animals that were allowed to die from poisoning with viosterol. However, they are considerably more extensive than the lesions produced by some other workers who allowed the animals to die from massive doses of viosterol. Three and a third months after their production the lesions were extreme, and I think that they represent about the maximal degree of involvement compatible with return to apparent health. In many of the lesions the apparent proportion of hyalinized tissue to microscopically visible calcium was greater than in comparable lesions in the previous experiments; this suggests

that some of the calcium had been reabsorbed during the three or four months after the cessation of medication. Naturally, the vascular deformity would be expected to remain despite any tendency toward reabsorption of the calcium. The vascular sclerosis produced in these experiments was not the result of spontaneous atherosclerosis, which sometimes occurs in older rabbits. Also, the experimental lesions did not in any way resemble the changes found in the aortas of rabbits following the administration of cholesterol or nonirradiated ergosterol. This study seems to show a method of producing permanent severe sclerosis of the aorta and renal vessels.

AUTHOR'S SUMMARY.

STATUS MARMORATUS, ETIOLOGY AND MANNER OF DEVELOPMENT. K. LÖWENBERG and WILLIAM MALAMUD, Arch. Neurol. & Psychiat. 29:104, 1933.

Status marmoratus is characterized by the appearance in the corpus striatum of stripes of myelin which form a dense network containing in its meshes lighter islands of degenerated nerve tissue, for the most part replaced by glia. The authors report four cases, three of which were studied histologically. Formation of scars of glia tissue and their myelinization took place in the corpus striatum, optic thalamus and cortex. The lesions were rather diffuse. In one case the process spared the basal ganglions and was confined to the cortex. The process is, according to the authors, inflammatory and not a developmental anomaly.

G. B. HASSIN.

THE BRAIN IN A CASE OF MOTOR APHASIA IN WHICH IMPROVEMENT OCCURRED WITH TRAINING. H. DOUGLAS SINGER and A. A. LOW, Arch. Neurol. & Psychiat. 29:162, 1933.

Right hemiplegia including the face developed in a woman one day following a difficult confinement. The paralysis was accompanied by aphasia, with inability to talk but with apparent understanding of speech. Two years after the stroke the patient was taught to pronounce simple, monosyllabic words, and later more complicated words; she was also trained in using the extremities. Death occurred twenty-five years later. Necropsy revealed a cavity on the left side involving the second and third frontal convolutions, which extended to the corpus striatum. Microscopic studies revealed an old process of destruction of the areas which preside over the function of speech; yet the latter improved considerably with persistent training.

G. B. HASSIN.

SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD. N. W. WINKELMAN and CHARLES DAVISON, Arch. Neurol. & Psychiat. 29:317, 1933.

The authors studied the changes in the spinal cord in twenty-five cases of pernicious anemia with a view to determining whether such changes are inflammatory, degenerative or of some other origin. In five cases, in some of which the duration of the disease was from four to seven years, the blood vessels exhibited perivascular infiltration. The type of the infiltrating cells was determined by using differential stains—sudan IV, for instance, for fat, and a nuclear stain, such as the Unna-Pappenheim stain, for lymphocytes or plasma cells. The predominance of fat in subacute combined degeneration of the cord shows it to be a degenerative process; the prevalence of lymphocytes and plasma cells indicates inflammation. The presence of both, as in dementia paralytica, denotes a combined process (inflammatory and degenerative).

G. B. HASSIN.

NERVE DEGENERATION IN POLIOMYELITIS. HERMAN CHOR, Arch. Neurol. & Psychiat. 29:344, 1933.

Chor studied, by means of a slight modification of the pyridine-silver method of Ranson, the changes in the motor nerve endings as they occur in experimental poliomyelitis of monkeys. He contrasted the changes with those in normal animals

and in monkeys in which the nerves had been cut. The changes in the muscular nerve endings in poliomyelitic monkeys were found to be analogous to those obtained after experimental sectioning of the nerves: Swelling and thickening of the terminal arborizations of the axons occur, followed later by fragmentation of the neurofibrils and swelling and breaking up of the myelin and axons with final granular transformation of the motor end-plates. The difference is that in poliomyelitis the changes, which begin with the onset of the paralysis, are not as diffuse as those in experimentally produced degeneration (by nerve section). There are in poliomyelitis many normal looking end-plates mixed with some which exhibit various stages of degeneration. Regenerative phenomena occur late, two months after the lesion. The variety and the degree of the changes in the end-plates depend on the condition of the ventral horn cells, being secondary to it. That they are not primary, that is, are not, like the changes in the ganglion cells, due to the direct action of the poliomyelitic virus, is proved by the fact that saturation of the muscles themselves with the virus and through them of the motor nerve endings failed to produce in the latter demonstrable histologic changes.

G. B. HASSIN.

ABSCESS AND THROMBOSIS OF THE SUPERIOR LONGITUDINAL SINUS. GEORGE B. HASSIN, *Arch. Neurol. & Psychiat.* 29:359, 1933.

In a man in whom an intracranial streptococcic infection of sixteen months' duration developed following a mastoid lesion, necropsy revealed an abscess of the longitudinal and sagittal sinuses and thrombosis of the frontal part of the former. It was possible to follow the successive stages of the transformation of the abscesses into a connective tissue scar and to demonstrate the rôle played by various mesodermal elements, especially the histiocytes and fibroblasts. The thrombus was separated from the dura by elastic fibers, and over the lateral sinuses the dura was studded by small abscesses. The pia showed no changes; the arachnoid exhibited masses of mesothelial cells, and in the brain, especially in the frontoparietal region, neuronophagia and satellitosis were present. Signs of hydrocephalus or hydrops of the brain were absent, which speaks against the theory that the spinal fluid, after passing through the pacchionian bodies, is received by the longitudinal sinus for final absorption. Failure to do this should, if the theory is correct, invariably lead to external and internal hydrocephalus—which were absent; neither were changes present in the pacchionian bodies.

AUTHOR'S SUMMARY.

ADDISON'S DISEASE WITH SO-CALLED ATROPHY OF THE ADRENAL CORTEX. G. LYMAN DUFF and C. BERNSTEIN, *Bull. Johns Hopkins Hosp.* 52:67, 1933.

Five cases of Addison's disease, in four of which the patient had been treated with extract of suprarenal cortex, are reported. All of the patients showed more or less complete "atrophy" of the suprarenal cortex. The destructive process in the suprarenals consisted of a progressive necrosis of cortical cells with collapse of the stroma. In two cases there was regeneration of cortical tissue. The medulla was affected much less, usually showing only a slight increase in the density of the fibrous framework and some shrinkage of the medullary cells. Lymphocytic infiltrations were constantly present in the suprarenal medulla and among the remnants of cortical tissue. Lymphocytic infiltrations in various situations constituted the most constant findings in association with the suprarenal lesions. Marked hyperplasia of lymphoid tissue was not present. No lesions were found for which the treatment with extract of suprarenal cortex could be held responsible. Consideration of the possible etiologic factors in the suprarenal lesions leads to the conclusion that a circulating toxin of unknown origin and nature was probably the causative agent. A brief account is given of observations on four cases in which the early stages of destruction of the suprarenal cortex were found but no clinical evidence of Addison's disease. The findings indicated that the primary suprarenal lesion is in the cortex and that the three zones of the cortex differ in their susceptibility to damage.

AUTHORS' SUMMARY.

CONGENITAL ATRESIA OF THE SMALL INTESTINE. F. LAESSING, Arch. f. Kinderh. 97:1, 1932.

This article includes a review of the literature, a report of a case and a discussion of the subject. In a 3 day old child, born at full term, who died of icterus and bronchopneumonia, the stomach, duodenum and proximal 20 cm. of the jejunum were dilated. Twenty centimeters from the duodenojejunal flexure, the bowel was narrowed and twisted on its axis, and a swollen, tumid loop passed through a small, smooth-edged opening in the mesentery and hung free in the abdomen below. Histologically there were two bandlike constrictions, with loss of the lumen, mucosa and submucosa. The lumen between was lined by normal mucosa and contained mucus. The distal portion of the bowel was dilated and contained whitish masses. At the point of narrowing there were hypertrophy of the muscular coats, proliferation of connective tissue and cells containing blood pigment. The author does not consider that there was enough evidence of damage to account for volvulus due to peristaltic activity, nor was the nature of the occlusion suggestive of an arrest of epithelialization. He believes that the condition was due to trauma, "in the broadest sense of the word," occurring before the fifth month of fetal life. The nature of the trauma is an open question.

J. STEWART.

CENTRAL TUBERCULOUS MYELITIS. M. B. SCHMIDT, Beitr. z. path. Anat. u. z. allg. Path. 87:314, 1931.

In a 58 year old patient with the clinical appearance of having a tumor of the cord there was discovered a syringomyelia-like tuberculous lesion. There was an obturating tuberculous arteritis with secondary, noncaseating ischemic myelomalacia.

W. S. BOIKAN.

EFFECT OF UNILATERAL INTRA-AURICULAR RISE IN PRESSURE ON THE AURICULAR SEPTUM. H. MILLER, Beitr. z. path. Anat. u. z. allg. Path. 87:365, 1931.

A long continued rise of pressure in one auricle leads to thinning and bulging of the membranous part of the auricular septum toward the side of lower pressure. In mitral stenosis this bulge may assume aneurysmal proportions. With a rise of pressure on the right side from failure of the right side of the heart, this bulge disappears. The author found one case of emphysema with aneurysmal dilatation into the left auricles. He further points out that a persistent eustachian valve forms, together with the atrial septum, a runway which directs the blood from the inferior vena cava toward the foramen ovale and may be the pertinent factor in the maintenance of the patency of the foramen and in the genesis of paradoxical emboli.

W. S. BOIKAN.

PEPTIC ULCER IN MECKEL'S DIVERTICULUM. G. SCHAAFF, Deutsche Ztschr. f. Chir. 238:78, 1932.

Gastric mucosa was found in six of fifty cases of Meckel's diverticulum, and occasionally in omphalomesenteric cysts and fistulas. Hydrochloric acid and pepsin have been found in such cases, which indicates normal gastric mucosa function as well as structure. The ulcers present were similar histologically to gastric ulcers, and in one case the free hydrochloric acid was 40 and the total 70. The clinical history so closely simulates that of gastric or duodenal ulcer that preoperative diagnosis is difficult or impossible. The aberrant gastric mucosa secretes simultaneously with the stomach, and therefore pain appears soon after meals and is relieved by the alkaline intestinal fluid. The most constant features of the condition are the massive hemorrhage, bright red and often dark stools, colicky pains and severe peritonitis if perforation occurs.

J. STEWART.

FATAL HEMORRHAGE FROM ESOPHAGEAL VARIX IN THE ABSENCE OF ABNORMALITY OF THE LIVER. J. NOCHIMOWSKI, Frankfurt. *Ztschr. f. Path.* **43**:463, 1932.

In two persons with esophageal varix the liver was normal and no cause for the varices was found.

RELATIONSHIPS BETWEEN LEUKEMIA AND GOUT. ARTHUR SCHULTZ, Virchows Arch. f. path. Anat. **280**:519, 1931.

In a case of gout with typical deposits of urates in the joints, tendon sheaths and bursae, there were extensive leukemic infiltrations in the liver, spleen, lymph nodes, bone marrow and kidneys, with an aleukemic blood picture. In leukemia the kidneys occasionally have deposits of ammonium urate in the form of spheroliths in the lumens of the collecting tubules, similar to so-called uric acid infarcts in the new-born. In gout, however, the kidney has in the interstitial tissue deposits of uric acid which change to sodium urate and become organized by foreign body granulomas. The latter picture was found in this case. A relationship between leukemia and gout is considered. Three methods for the histologic demonstration of uric acid and urates are presented.

PERRY J. MELNICK.

CYSTICERCUS IN THE BRAIN. P. HEILMANN, Virchows Arch. f. path. Anat. **286**:176, 1932.

In five thousand necropsies, Heilmann has encountered a cysticercus in the brain six times. In three of the cases the cyst was situated in the fourth ventricle and in one case, in the third ventricle; in all of these it was the immediate cause of death by occlusion of the foramen of Magendie or of the aqueduct of Sylvius. In the fifth case the cyst was racemose, involved the region of the sylvian fissure, and was not the cause of death. In the sixth case the cyst occluded the foramen of Monro and caused death. This case is reported in detail because the author was not able to find a recorded instance of occlusion of the foramen of Monro by a cysticercus, although the statement is made that such a condition occurs.

O. T. SCHULTZ.

ILEOCOLIC HERNIA. K. G. ROSCHDESTWENSKIJ, Virchows Arch. f. path. Anat. **286**:249, 1932.

In 1923 and 1924, K. Z. Jazuta, a professor at the University of Rostow, described in the human fetus from 60 to 70 mm. long a shallow pocket or depression of the mesial surface of the mesentery of the cecum, which he named recessus ileocolicus. It is present in 88 per cent of fetuses from 200 to 300 mm. long, in 78 per cent of fetuses from 300 to 520 mm. long, in 60 per cent of infants less than 1 year old, in 20 per cent of children from 1 to 5 years old and in 10 per cent of children from 5 to 10 years old. Jazuta saw the pocket only once in an adult; he expressed the belief that in that instance it might be the site of an extra-peritoneal hernia. Such a hernia in an adult is described by Roschdestwenski; it was found by chance during anatomic study.

O. T. SCHULTZ.

Pathologic Chemistry and Physics

DETECTION AND DETERMINATION OF ORGANIC ACIDS IN BLOOD SERUM. H. BRUHL, Klin. Wchnschr. **12**:72, 1933.

Organic acids in 2 cm. of blood serum were determined by making a graph of the electrometric titration curves of the ultrafiltrate of the serum. The organic acids of serum are increased in pregnancy and in uremia; the acids in pregnancy, however, differ from those in uremia. Increases were also found in patients with convulsions and in patients on a ketogenic diet. A decrease in the organic acids

occurred in children with florid rachitis. A comparison of the arterial and venous blood of the brain showed that the organic acids disappear in the brain in tetany.

D. O. ROSBASH.

ACID-BASE BALANCE AND EDEMA. O. L. E. DE RAADT, *Klin. Wchnschr.* **12**:224, 1933.

Edema is due to a disturbance in the acid-base equilibrium of the blood and not to a lowering of the colloidal osmotic pressure of the blood by a decrease in proteins. The decrease in the serum protein of the blood causes alkali deficiency through loss of sodium bound to the protein and through loss of the buffer action of the protein. The resulting acidosis is not compensated by the kidneys. Edema accompanying decompensation of the heart does not differ from nephritic edema. There is acidosis because of circulatory obstruction, a lowered excretion of carbon dioxide and a decrease in the formation of ammonia by the kidneys. The end-products of metabolism are acid (organic acids and carbon dioxide). In cardiac disease the acidosis is greatest when circulatory disturbances are maximum, and as a result edema appears first in the lower extremities. In edema accompanying heart disease the blood contains as much ammonia as it does in nephritic edema. The change of permeability of the capillaries in edema is a result and not a cause, since the formation of ammonia in the tissues alters the permeability of the capillaries.

D. O. ROSBASH.

RADIOACTIVITY OF PATHOLOGIC TISSUES AFTER INTRAVENOUS ADMINISTRATION OF THORIUM. G. JOANNOVIĆ, D. K. JOVANOVIĆ and X. CHAHOVITCH, *Virchows Arch. f. path. Anat.* **287**:127, 1932.

Previous experiments on rabbits showed that after the intravenous administration of radioactive thorium salts, the liver, spleen, epithelium of the lungs and bone marrow become radioactive. Experimentally produced tar cancers and papillomas exhibited no radioactivity. To determine whether normal tissues that undergo pathologic alteration retain their ability to store radioactive substances, a small series of experiments was performed. Two dogs which had been rendered diabetic by resection of the pancreas received radioactive thorium intravenously. In other dogs parenchymatous changes were brought about by phosphorus poisoning. The animals and their controls were killed twenty-four hours after the injection of thorium. No change was noted in the radioactivity of the liver, the spleen and the epithelium of the kidney and lung in the animals in which pathologic changes had been produced. The determination of radioactivity was not quantitative, but was judged by the ability of the tissues to affect the photographic plate.

O. T. SCHULTZ.

ENZYME CONTENT OF THE PANCREAS. J. BALÓ and L. LOVAS, *Virchows Arch. f. path. Anat.* **288**:326, 1933.

The enzyme content of the pancreas was determined in a series of seventy necropsies on persons who died of a variety of diseases. In twenty only lipase and trypsin were found; in the remaining fifty diastase was also found. In general the three ferments varied *pari passu* with each other. In sepsis, trypsin was reduced to a greater degree than were the other two ferments. In wasting, cachectic diseases, the three ferments were reduced. Lipase was increased in two cases with fat necrosis; Baló and Lovas suggest that increased lipase content may predispose to fat necrosis.

O. T. SCHULTZ.

PHANEROSIS OF FAT. N. M. NIKOLAJEW and S. LODYSHENSKAJA, *Virchows Arch. f. path. Anat.* **288**:554, 1933.

A series of simple but ingenious experimental technical procedures for the visualization of cellular lipoids led Nikolajew and Lodyshenskaja to some important

conclusions relative to lipid metabolism. They believe that the tissue cells may absorb preformed lipoids directly from the blood and tissue fluids; this is the usual normal physiologic process. Or the cells may take up protein-lipoid complexes, which may be acted on by intracellular ferments, the lipid fraction becoming stainable by the usual methods or after treatment with ammonium chloride. The second process is the one that occurs under pathologic conditions. Toxins, poisons and other noxious factors lead to the liberation of protein-lipoid complexes, which are taken up by tissue cells. In the latter, fermentative destruction of the complex may have diverse effects on the cell. The water and protein balance of the cell may be disturbed, a condition that manifests itself morphologically as parenchymatous, hyaline or vacuolar degeneration. Or the lipid element of the complex may be visualized, a state that evidences itself morphologically as fatty degeneration. Nikolajew and Lodyshenskaja accept Ciaccio's classification of the cellular lipoids into anabolic and histogenous, but subdivide the anabolic lipoids further into the free and the bound. Under both normal and abnormal conditions, endogenous lipoids derived from broken-down red corpuscles and other cells play an important part in cellular metabolism.

O. T. SCHULTZ.

PHYSICOCHEMICAL CHANGES OF PARENCHYMATOUS DEGENERATION. V. UHER, *Virchows Arch. f. path. Anat.* **288**:562, 1933.

In this continuation of previously reported studies of the physicochemical changes of parenchymatous degeneration, Uher used suspensions of liver cells and determined the following: sodium, potassium, calcium and magnesium; total nitrogen and coagulable protein; dialysable nitrogen and amino-acids; the protein precipitation of extracts in various concentration by a variety of precipitants, and the colloid protective action for gold and mastic sol. The content of dialysable nitrogen and amino-acids was increased; this is interpreted as indicative of a qualitative change, rather than a merely quantitative one, in the protein of the cell. An increase of the monovalent ions over the bivalent ions in the ratio $\text{Na} + \text{K} : \text{Ca} + \text{Mg}$ is held to explain the swelling of the cells. Changes in the protein precipitation and colloid protective curves of the hydrophil sols of the extracts are evidence of changes in the nature of protein of the cells and its derivatives.

O. T. SCHULTZ.

NATURAL MELANINS. HEINRICH WAELSCH, *Ztschr. f. physiol. Chem.* **213**:35, 1932.

The melanin of the choroid and fuscine of horse's eyes and human melanin in the liver from metastatic malignant melanomas of the eye, which are characterized by a positive Tormählen reaction in the urine, were investigated. Choroidal melanin contains traces of iron; the other melanins are free from it. All melanins contain sulphur in considerable quantities. The chromophoric groups of the sarcoma melanins have the same elementary composition. The choroidal melanins and fuscins have different chromophoric groups and differ in this respect also from each other. The melanins contain a protein substance which cannot be digested and which can be isolated by prolonged hydrolysis by hydrochloric acid.

WILHELM C. HUEPER.

Microbiology and Parasitology

CYSTS OF THE DYSENTERY-PRODUCING *ENDAMOEBIA HISTOLYTICA* IN A BALTIMORE DOG. JUSTIN ANDREWS, *Am. J. Trop. Med.* **12**:401, 1932.

A case of natural chronic amebic infection in a Baltimore dog, in the dejecta of which cysts were found, is recorded. From the evidence, it seems strongly probable that the organism involved was *Endamoeba histolytica*, and that the dog may be in nature an occasional carrier of this parasite, constituting, in this condition, a reservoir of amebiasis for man and dogs.

AUTHOR'S SUMMARY.

TYPES OF TUBERCLE BACILLI ISOLATED FROM HUMAN LESIONS. R. M. PRICE,
Am. Rev. Tuberc. **25**:383, 1932.

Bovine tuberculosis is an almost negligible factor in the tuberculosis of human adults. The bovine tubercle bacillus is a factor of considerable importance in the tuberculosis of childhood (in Canada); 13.6 per cent of nonpulmonary tuberculosis, leading to disablement, operation and the necessitation of prolonged and costly treatment, with doubtful results at the outcome, is caused by the bovine tubercle bacillus. The disease is milk-borne and is preventable by effective pasteurization of milk. In Toronto, where pasteurization has been compulsory since 1915, not a single case of bovine infection has been encountered (1915-1930).

H. J. CORPER.

A COMPARISON OF TISSUE REACTIONS TO TESTICULAR INOCULATION OF ACID-FAST BACILLI. ESMOND R. LONG and ARTHUR J. VORWALD, Am. Rev. Tuberc. **25**:614, 1932.

A wide range of virulence for the guinea-pig was disclosed among the acid-fast bacilli—human (H 37), bovine (Vallee, 1920), avian (Van Es, 1921) frog bacillus (*M. ranæ*) (Moeller, 1900), timothy grass (*Mycobacterium phlei*) (Moeller, 1904)—injected into the testes of guinea-pigs. These strains were previously used for chemical study by other investigators. Little difference was to be seen in the effects of the human and bovine types used as 0.1 mg. in 0.3 cc. The immediate reaction to these micro-organisms was more intense than that toward the less virulent strains, and the end-result was extensive necrosis with suppuration. The gross and microscopic pictures as early as six hours after inoculation forecast with considerable accuracy the outcome at four weeks. The strain of avian bacillus used possessed unmistakable virulence, although of much lower degree than that of the human and bovine types. The lesions produced by the frog bacillus also appeared to have a progressive tendency for a time. At two weeks, although not at four, the cellular reaction was still increasing, and at that time was much more intense than that produced by the saprophytic smegma and timothy bacilli. Moreover, while no caseation necrosis developed, the inflammatory reaction was of sufficient intensity to cause profound atrophy of the seminiferous tubules. To smegma and timothy bacilli, the reaction diminished from the third day on, and necrosis did not develop. If both testes were inoculated, the one with the human bacilli and the other with smegma bacilli, there appeared to be an initial difference in the gross reaction to the tubercle bacilli. Hyperemia was absent during six to twenty-four hours, but the ultimate effect of the tubercle bacilli in the presence of the small dose (0.1 mg.) of smegma bacilli in the opposite testis was unchanged, extensive tuberculous damage with the usual suppuration resulting. On the other hand, the presence of progressive tuberculosis seemed to make the tissues less tolerant to the smegma bacillus.

H. J. CORPER.

EXPERIMENTAL TUBERCULOSIS IN THE ALBINO RAT. M. MAXIM STEINBACH,
Am. Rev. Tuberc. **26**:52, 1932.

The normal rat is highly refractory to infection with the human and the bovine tubercle bacilli. Age is not a factor in this immunity. The normal rat is but slightly susceptible to intraperitoneal injection of large doses of avian bacilli. Avitaminosis decreases the resistance of the albino rat to the avian tubercle bacilli, but not to the mammalian types. Suprenalectomy decreases the resistance of the rat to both avian and bovine tubercle bacilli, but does not affect the animal's resistance to human bacilli. Parathyroidectomy is a factor in lowering the resistance to the bovine but not to the human strain. Thyroid-parathyroidectomy renders the rat susceptible to infection with the human as well as with the bovine type of bacilli. Macroscopic and microscopic tuberculosis in the rat does not differ from that seen in other experimental animals, or in man. Pseudotuberculosis, frequent in the normal rat, can be readily differentiated histologically from true tuberculosis.

H. J. CORPER.

THE CALCIFICATION OF EXPERIMENTAL INTRAABDOMINAL TUBERCULOSIS. TOM DOUGLAS SPIES and W. REECE BERRYHILL, *Am. Rev. Tuberc.* **26**:275, 1932.

The administration of repeated large doses of viosterol to guinea-pigs following intraperitoneal inoculation of tubercle bacilli caused calcification of many tubercles. The calcium was deposited in the renal tissues of the tuberculous animals to a much more marked degree than in the kidneys of normal animals receiving still larger doses of viosterol. This suggests that there may be some underlying factor which is related to the tuberculous process and which affects calcium metabolism. It is suggested that a diet high in vitamin D might be beneficial in intraperitoneal tuberculosis.

H. J. CORPER.

BACILLEMIA IN TUBERCULOSIS. LITA SHAPIRO, *Am. Rev. Tuberc.* **26**:418, 1932.

In 167 cases of tuberculosis tested with the Löwenstein technic there were only 7 positive blood cultures (4.2 per cent). None of the 28 cases of rheumatic fever and chorea gave positive blood cultures.

H. J. CORPER.

TUBERCULOSIS IN THE INDIAN. HERBERT A. BURNS, *Am. Rev. Tuberc.* **26**:498, 1932.

The Indian has a death rate from tuberculosis ten times greater than his white neighbor. Racial mixing has not seemed to reduce the rate of infection with tuberculosis or the mortality from it in the Indian population. The rate of infection is much higher among the Indian than the white school children living in the same county. There are no marked differences in the clinical types occurring among the various degrees of mixed bloods, full bloods and the whites. The opportunity for contact over a long time seems to be the most important element explaining the prevalence of, and the high death rate from, tuberculosis. Tuberculosis in the Indian does not differ in any important essential from other communicable diseases. The Indian constitutes an important reservoir of infection which must be controlled to prevent the spread of the disease to the non-Indian population.

H. J. CORPER.

BLENNORRHAGIC KERATOSIS. STANLEY O. CHAMBERS and GEORGE F. KOETTER, *Arch. Dermat. & Syph.* **27**:411, 1933.

A case of blennorrhagic keratosis is reported, with multiple biopsies. The earliest cutaneous lesion was a minute dull red papule which became pustular in its center. A crust developed at the center of the pustule, spreading peripherally until the entire lesion was crusted. The periphery of the lesion remained pustular. Gray flat papules were present over the hard palate, the sides of the tongue and the buccal mucous membrane. Microscopic examination showed the earliest change in the superficial dermis in the form of a perivascular lymphocytic infiltration. The epidermis was involved secondarily, first with a marked edema and later with invasion of the epidermis by leukocytes. This was followed by focal necrosis in the superficial epidermis, which extended peripherally. Superficial crusting occurred, which became more and more extensive until, when activity had ceased, the entire superficial epidermis was replaced by a crust which ultimately separated, leaving smooth, hyperpigmented skin. During one exacerbation of clinical symptoms the patient had severe iritis and conjunctivitis of the left eye. This was followed by marked edema of the retina, and the entire process cleared up in about four weeks, with deposits of pigment on the anterior capsule of the lens. The complement-fixation test for gonorrhea was strongly positive. Efforts to identify the gonococcus from cultures and smears from the blood gave negative results. Aspirated material from lesions in all stages of development failed to show the gonococcus. Emulsified tissue, when placed on culture mediums, did not show the gonococcus. Attempts to bring about the development of new lesions by auto-inoculation were unsuccessful.

S. W. BECKER.

STUDIES IN EXPERIMENTAL SYPHILIS. A. M. CHESNEY, T. B. TURNER and F. H. GRAUER, Bull. John Hopkins Hosp. **52**:145, 1933.

Rabbits infected with one strain of *Spirochaeta pallida* (Nichols strain) and treated comparatively late in the course of their disease, i. e., from six to eight and two-thirds months after the first inoculation, were subsequently inoculated with a different strain of *Spirochaeta pallida* (strain F) by depositing the virus on the intact genital mucous membrane. Under these conditions, 46 per cent of the test animals were successfully infected a second time. In an equal number of control normal animals inoculated in a similar manner, the incidence of positive inoculations was 62 per cent. The conclusion is drawn that the immunity which develops in rabbits during the course of a syphilitic infection is strain-specific even when tested as outliped, that is to say, in a manner which favors the host rather than the inciting agent. The occurrence of syphilitic reinfection in man and its bearing on the reported experiments with rabbits are discussed.

AUTHORS' SUMMARY.

VARIANTS OF A STRAIN OF *BACILLUS DYSENTERIAE*. A. COMPTON, J. Infect. Dis. **51**:428, 1932.

Two naturally occurring variants, opaque (O) and translucent (T), of an organism of the Gay-Harris group of *B. dysenteriae*, met with in cases of acute bacillary dysentery at Alexandria, are described. Sharply defined differences between the variants in cultural, morphologic, serologic and lytic properties are recorded, with less sharply defined differences in virulence, immunizing power and susceptibility to the bactericidal action of normal serum. There appears to be no detectable difference between them in sensitiveness to salt or in biochemical properties. Characteristic lenticular or fusiform bodies, which are a feature of colonies of the O variant on agar, are discussed. They are thought to be of the nature of bacterial aggregates, and may be a cause of the fluorescence. The usual confirmatory tests for "smoothness" and "roughness" of bacterial variants—sensitiveness to salt, clouding of broth and specific agglutination—find no application as distinguishing tests of "opaqueness" and "translucency." Instead, the differential confirmatory tests for this type of bacterial variation, as based on the present study, are internal lenticular bodies in the colony structure, fluorescence by obliquely transmitted artificial light and phage action.

AUTHOR'S SUMMARY.

ACIDURIC AND ACIDOGENIC MICRO-ORGANISM IN DENTAL CARIES. W. H. TUCKER, J. Infect. Dis. **51**:444, 1932.

Cultures prepared in acid broth (p_H 5) from scrapings of the surfaces of the teeth of 422 children yielded micro-organisms of some type in practically every case. Streptococci of various types were isolated most frequently, but *Lactobacillus acidophilus*, *Staphylococcus albus* and yeasts also developed in the acid medium. An attempt was made to correlate the incidence of dental caries with the occurrence of some one type of aciduric micro-organism. This attempt was unsuccessful. Aciduric streptococci were found in the mouths of practically all of the children irrespective of the incidence of dental caries and irrespective of the ingestion of citrus fruit juice. *L. acidophilus* was found most frequently and most consistently in the mouths of children whose teeth contained three or more cavities. Some relationship appears, therefore, to exist between the persistent presence of *L. acidophilus* and cavities in the teeth. This micro-organism was not, however, always found, even in those cases in which there was shown a high susceptibility to dental caries. If one is to conclude that *L. acidophilus* is the cause of dental caries, one must always find this organism associated with dental caries. This I was unable to do. *L. acidophilus* occurred rather frequently and consistently in the mouths of children who had never had any dental caries, or who had developed no new carious lesions for two years. From this it appears that *L. acidophilus* is not an obligate producer of dental caries.

AUTHOR'S SUMMARY.

EFFECT OF VITAMINS A AND D IN INFECTION BY *SALMONELLA ENTERITIDIS*.
L. S. McCLUNG and J. C. WINTERS, *J. Infect. Dis.* **51**:469 and 475, 1932.

A marked increase in susceptibility to infection with *Salmonella enteritidis* injected intraperitoneally was shown in a group of white rats fed on a vitamin A-free diet for a period of seven weeks, as compared with a control group similarly infected. A slight increase in susceptibility to infection by intraperitoneal injection of *S. enteritidis* was shown by a group of white rats kept for a period of seven weeks on a diet low in vitamin D, as compared with a similar group of controls kept during the same period on an adequate diet and similarly infected. This decrease in resistance to infection is not as great as that previously shown to be brought about by a deficiency of vitamin A in the diet.

AUTHORS' SUMMARIES.

ADENOTONSILLECTOMY AND COMMON COLD IN ADULTS. W. M. GAFAFER,
J. Infect. Dis. **51**:489, 1932.

A group of 179 adults was observed for thirty-five weeks from Sept. 29, 1929, to May 31, 1930, and every effort was made to secure reports of all attacks of disease of the upper respiratory tract (common cold). Of these adults, 123 showed tonsils and adenoids, and 56 did not. The group with tonsils and adenoids and the group without tonsils and adenoids presented no significant difference with respect to frequency, severity or type of attack of disease of the upper respiratory tract (common cold).

AUTHOR'S SUMMARY.

Immunology

THE ARTHUS PHENOMENON. I. HARRISON TUMPEER and E. J. COPE, *Am. J. Dis. Child.* **45**:343, 1933.

In a syphilitic patient with the Arthus phenomenon resulting from injections of horse serum (diphtheria antitoxin and toxin-antitoxin), precipitins to horse serum were demonstrated. The patient's serum contained a transferable substance which was toxic for rabbit and guinea-pig skin. This substance interacted with horse serum (diphtheria antitoxin) when passively transferred to a rabbit or a guinea-pig. It was capable of further demonstration by the technic of Shwartzman. The serum of the patient probably contained a transferable substance which produced a toxic interaction with donor serum in the skin of the rabbit. Controls with essentially similar serums from members of the same family similarly treated but not manifesting the Arthus picture were negative. The fatal reaction to transfusion, despite agglutinin and hemolysin compatibility, was due to other changes in the patient's blood incident to the Arthus phenomenon.

AUTHORS' SUMMARY.

THE NEUTRALIZATION OF POLIOMYELITIS VIRUS BY THE SERUM OF LIBERIAN NEGROES. N. P. HUDSON and E. H. LENNETTE, *Am. J. Hyg.* **17**:581, 1933.

The experimental finding that eighteen of the nineteen samples of serum from Liberian Negroes had a virucidal capacity is comparable with the results of similar analyses in the United States. We cannot ascertain what the incidence of this disease is among the Negro tribes from which the persons came who furnished the serum. Some observers report probable cases among the Liberian natives, and the acute form of the disease is recorded in other parts of tropical West Africa. On the basis of the situation in the United States, it appears that the results are compatible with a wide distribution of the poliomyelitis virus. The proper interpretation of the experimental findings depends on the significance of the neutralization test as a specific immune reaction. We failed in our attempt to find in a Negro population little exposed to whites of the temperate zone a group of persons giving negative neutralization tests, which might act as a control in analyses of

human serum elsewhere. We may conclude that the problem of the interpretation of the virucidal property of normal adult serum of Liberian Negroes is the same as in the temperate zone.

AUTHORS' SUMMARY.

THE SENSITIZATION OF GUINEA PIGS AND THE PRODUCTION OF ALLERGY AND ANAPHYLAXIS TO TUBERCULOPROTEIN. H. S. REICHLE and HARRY GOLDBLATT, *Am. Rev. Tuberc.* **27**:291, 1933.

Normal guinea-pigs received intracutaneous injections of from 1 to 10 per cent solutions of old tuberculin and various adjuvant substances, such as eye fluid of normal guinea-pigs and horse serum. When these animals were retested with old tuberculin within from three to eight days after the sensitizing injection, they responded in a fashion typical of bacterial allergy; 55 of 102 animals showed this phenomenon. The cutaneous reactions were of the prolonged, allergic type, and although vesiculation and ulceration were never seen, they were otherwise analogous to those observed in tuberculous animals. The same reaction was obtained with Seibert's pure tuberculoprotein. At an early stage of an experiment the animals were not sensitive to glycerin broth, but after repeated injections with old tuberculin sensitivity to glycerin broth developed. In some of the animals a positive Long testicular test for allergy to tuberculin was obtained; in others a strong anaphylactic sensitivity to tuberculin was demonstrated by means of the Dale test. It is probable that an adjuvant substance is not a necessary factor and that the essential element in all previous reports of unsuccessful artificial sensitization to tuberculin has been the tuberculin itself. Other investigators may not have been able to substantiate earlier observations because of the failure to recognize the incubation period, the use of animals weighing less than 500 Gm., which are not easily sensitized, and the lack, at that time, of an objective measure of allergy, such as the Long testicular test.

H. J. CORPER.

THE EFFECT OF TUBERCULIN ON SPERMATOOZOA FROM NORMAL AND TUBERCULOUS GUINEA PIGS. LILIAN C. DONALDSON and ARTHUR J. VORWALD, *Am. Rev. Tuberc.* **27**:401, 1933.

By the motility test spermatozoa from tuberculous animals could not be shown to be hypersensitive to strong concentrations of tuberculin or to purified tuberculin-protein fractions. The method, therefore, is not a suitable one for testing the potency of tuberculins. Spermatozoa from tuberculous animals are apt to be slightly less motile and to sustain their motility less well in Locke's solution than spermatozoa from noninfected animals. Strong concentrations of synthetic-medium tuberculin caused an initial acceleration of motility in spermatozoa from normal and tuberculous animals. A like acceleration is caused by similar concentrations of Long's synthetic medium alone. Strong concentrations of tuberculin cause a rapid decrease in the motility of spermatozoa from both normal and tuberculous animals; a similar but less rapid decrease is caused by equal concentrations of a synthetic medium. A carbohydrate fraction derived from tuberculin and a timothy-bacillus protein likewise lessened motility rapidly. Diphtheria toxin shows no effect on the motility of spermatozoa from either tuberculous or nontuberculous animals, other than an acceleration when very strong concentrations are used.

H. J. CORPER.

IMMUNE REACTIONS IN DIABETES. JOHANNES K. MOEN and HOBART A. REIMANN, *Arch. Int. Med.* **51**:789, 1933.

The development of agglutinins for typhoid bacilli after the vaccination of diabetic patients and normal persons was observed. In well patients with controlled diabetes, agglutinins developed in titers similar to those in normal persons used as controls. In patients with diabetes that was controlled with more difficulty, the agglutinin response was distinctly weaker. In patients with uncontrolled diabetes

with acidosis, the agglutinin response was poor; in a few cases no agglutinin for certain strains appeared. The coincidence of the increased susceptibility of severely ill diabetic patients and the deficiency of demonstrable antibodies suggests a causal relationship of the latter to the former condition.

AUTHORS' SUMMARY.

ACQUIRED IMMUNITY BY RABBITS TO SYPHILIS IS NOT DEPENDENT UPON ALLERGIC INFLAMMATION. A. R. RICH, A. M. CHESNEY and T. B. TURNER, *Bull. Johns Hopkins Hosp.* **52**:179, 1933.

Rabbits rendered immune to syphilis by inoculation with *Spirochaeta pallida* showed no allergic reaction whatever, whether macroscopically or microscopically, on intracutaneous reinoculation at periods ranging from twenty-eight to four hundred and eighty-two days after the primary, immunizing infection. On the contrary, the most striking phenomenon observed in the immune animals, as contrasted with the nonimmune controls, was always a remarkable indifference of the tissues of the former to the presence of the injected virus. Although it is well known that allergy to *Spirochaeta pallida* appears during human syphilitic infection and can also be induced in the rabbit, according to Noguchi, the present experiments demonstrate that allergic inflammation is not necessary for the operation of acquired immunity in syphilis.

AUTHORS' SUMMARY.

THE PREVENTION OF SPREAD OF BACTERIA IN THE IMMUNE BODY. A. R. RICH, *Bull. Johns Hopkins Hosp.* **52**:203, 1933.

In the nonimmune body pneumococci drift freely through the tissues from the site where they are deposited and readily invade the blood stream. In the actively or passively immunized body the bacteria are held sharply at the immediate site where they lodge. The local lesion in the immune body is therefore limited in size, and septicemia, with the attendant opportunity for metastatic infection, does not occur. The immediate local immobilization of the bacteria in the immune body is accomplished by the specific action of the immune antibody which, through its effect on the bacteria, causes them to remain fixed to the tissues at the site where they lodge until they can be surrounded and destroyed by the leukocytes. In this action the immune antibody performs an important and hitherto undemonstrated protective function. The process of immediate fixation of bacteria in the immune body occurs independently of inflammation and is in operation before any effective amount of inflammation is established at the site. Inflammation, when finally established, is, of course, of great importance in contributing to the localization of the infection and in effecting the destruction of the bacteria, but it is shown that the accelerated and exaggerated inflammation of allergy is not required for the successful performance of either of these two protective functions.

AUTHOR'S SUMMARY.

STUDIES ON THE PRECIPITIN REACTION. M. HEIDELBERGER and F. E. KENDALL, *J. Exper. Med.* **57**:373, 1933.

The products of partial hydrolysis of the specific polysaccharide of type III pneumococcus ranging from 550 to 1,800 in formula weight can be quantitatively freed from unhydrolyzed polysaccharide. The fractions yield specific precipitates with type III antipneumococcus horse serum but fail to precipitate homologous rabbit antisera, giving rise only to specific inhibition. The aldobionic acid, the structural unit of S, does not precipitate antisera. A possible explanation and a possible application of the findings are pointed out.

AUTHORS' SUMMARY.

ACTIVE IMMUNIZATION AGAINST TYPHUS FEVER. H. ZINSSER and M. RUIZ CASTANEDA, *J. Exper. Med.* **57**:381 and 391, 1933.

Vaccines consisting of formaldehydized Rickettsiae of Mexican typhus fever, obtained by our x-ray rat method, produce definite resistance in guinea-pigs to

subsequent infection with the virus of this disease. The resistance so produced amounts to complete immunity when the subsequent infectious dose is moderate, that is, when it consists of typhus blood or of tunica material in reasonable amounts (not more than one fourth of a tunica, i. e., roughly, from 100 to 250 infectious doses). When, as in the first experiment, excessive doses of infectious material were given, the vaccination protection was incomplete in two of the three animals. Subcutaneous vaccination is fully as effective as intraperitoneal, even when the subsequent infection is intraperitoneal. As in previously reported experiments, the vaccines made with the Mexican organisms conferred only partial and feeble protection against the European virus (Breinl strain). The injection of a horse with formaldehyde-killed and phenol-killed *Rickettsiae* from the Mexican virus induced the development of distinctive protective properties against the virus in the serum of the horse.

FROM AUTHORS' SUMMARIES.

NORMAL AND IMMUNE OPSONIN. H. K. WARD and J. F. ENDERS, *J. Exper. Med.* **57**:527, 1933.

In normal unheated human serum, virulent pneumococci may be prepared for phagocytosis by two separate antibodies acting in conjunction with the complement. One of these is the type-specific anticarbohydrate antibody reacting with the carbohydrate fraction of the pneumococcus. The other is probably also a type-specific antibody, but quite distinct from the former, and therefore must react with a different antigenic constituent of the bacterium. In the normal human serum heated to 56 C., these two antibodies may, after prolonged contact with the organism, promote phagocytosis of the pneumococcus without the adjuvant action of the complement. Although these two antibodies are equally effective in the phagocytosis by normal blood of organisms cultured for twenty-four hours, the anticarbohydrate antibody tends to become the predominant factor as the pneumococci approach the state in which they exist in the animal body. So far as we have been able to show, the anticarbohydrate antibody is the only antibody in immune serum which can induce phagocytosis. This substance by itself is active in a phagocytic system, but, just as in the normal serum, the complement enhances its effect. The failure to demonstrate the presence in the immune serum of an antibody distinct from the anticarbohydrate antibody and analogous to that found in the normal serum may be due to the experimental difficulty of removing all the anticarbohydrate antibody from a concentrated immune serum. Thus it is seen that a single well defined antibody (the anticarbohydrate antibody) may be responsible for the phagocytic action of normal unheated serum, normal heated serum, inactivated immune serum and immune serum activated by the complement. These facts appear to us to invalidate Neufeld's division of the phagocytic antibodies into bacteriotropins (antibodies, the phagocytic titer of which is not raised by the addition of the complement) and opsonic antibodies (antibodies comparable to the lysins, which are active only in the presence of the complement). The complement alone is incapable of inducing phagocytosis of the pneumococcus. In the phagocytic process, it appears simply to increase the speed at which the reaction takes place. Its rôle may be compared to that of a catalyst in a chemical reaction. On the basis of these findings, it is proposed that the term "tropin" be discarded as misleading and unnecessary, and that the term "opsonin" be retained to denote any heat-stable antibody which prepares bacteria for phagocytosis. Contrary to current usage, it would not suggest a combination of antibody with complement.

AUTHORS' SUMMARY.

A SEROLOGICAL DIFFERENTIATION OF HEMOLYTIC STREPTOCOCCI. R. C. LANCEFIELD, *J. Exper. Med.* **57**:571, 1933.

All except 2 of 106 strains of hemolytic streptococci isolated from man and other animals and from milk and cheese have been classified into 5 groups, which bear a definite relationship to the sources of the cultures. These broad groups

may be subdivided into specific types by methods discussed elsewhere. Classification in specific groups is made possible by employing two special reagents: extracts prepared by the treatment of the bacteria with hot hydrochloric acid, and serum of animals immunized with formaldehydized cultures. This differentiation is not detected by the agglutination reaction. The grouping agrees with that described by other investigators on the basis of cultural and biochemical characteristics. The group-specific substance present in strains of group A has been identified chemically as carbohydrate in nature. The chemical composition of the specific substances on which the specificity of the other groups depends has not been determined. It seems not unlikely, however, that all of them may belong in the general class of carbohydrates, each being chemically distinct and serologically specific in the individual groups.

AUTHOR'S SUMMARY.

SKIN TEST IN SERUM TREATMENT OF TYPE I PNEUMONIA. T. FRANCIS, JR., *J. Exper. Med.* **57**:617, 1933.

Tests of the skin were made with type I SSS in fifty-three cases of type I pneumococcus lobar pneumonia, in forty-eight of which the patients were treated with antipneumococcus type I serum. In all but one of the forty-six patients who recovered a positive, immediate reaction of the skin was obtained at about the time of recovery. In seven fatal cases the reactions were consistently negative, even in the presence of circulating type-specific antibodies. The cutaneous test has proved to be an extremely valuable guide to serum therapy, and a definite prognostic aid. It has distinct advantages over the agglutination reaction in that it is not merely an index of circulating antibodies. When positive, it invariably denotes that recovery has begun; when negative, it indicates further serum therapy. The mechanism of the positive skin test is closely related to that operative in recovery from pneumonia, and is apparently the resultant of antibody and tissue activity.

AUTHOR'S SUMMARY.

ANAPHYLACTIC SHOCK BY AZODYES. K. LANDSTEINER and J. VAN DER SCHEER, *J. Exper. Med.* **57**:633, 1933.

Experiments are described which show that anaphylactic shock can be induced in animals sensitized with azoproteins by injecting them with azodyes containing the same azo components as the sensitizing antigen. The anaphylactic reactions are specific and occur with quantities of the dyes as small as fractions of milligrams.

AUTHORS' SUMMARY.

CHANGES IN BACTERIAL VOLUME AS THE RESULT OF SPECIFIC AGGLUTINATION. F. S. JONES and R. B. LITTLE, *J. Exper. Med.* **57**:721 and 729, 1933.

Measurements indicate that bacterial antigens increase in volume as the result of specific agglutination. There is a general parallelism between the increase in antigenic volume and the concentration of the immune serum. The phenomenon is specific. There is no increase with normal serum; with absorbed serum the increase is slight and can be correlated with the presence of unabsorbed antibody. The effect is enduring, as shown by volumetric determinations on repeatedly washed, agglutinated bacteria.

When the increase in volume approximated 20 per cent, all the bacteria were agglutinated. We have attempted to correlate the volumetric increase with the quantity of protein absorbed by the organism during agglutination and have studied not only bacteria but also collodion particles first sensitized to antigen and then agglutinated with a precipitin specific for the antigen. The increase in volume of the collodion particles was small, and the quantity of protein adsorbed was relatively large. When two species of bacteria were agglutinated with their respective antisera the reverse was true; the apparent increase in volume was

much greater than the quantity of protein deposited during the reaction. There is, then, no direct correlation between the deposition of protein and the apparent increase in volume. Nevertheless, the results of the experiments here reported have suggested an explanation for the increase in volume.

AUTHORS' SUMMARIES.

INHERITED AND ACQUIRED FACTORS IN RESISTANCE TO INFECTION. L. T. WEBSTER, *J. Exper. Med.* **57**:793 and 819, 1933.

The experiments are a step in the analysis of inherent resistance to infection. Heredity has proved clearly to be an element of fundamental importance in determining the fate of individuals following primary exposure to a natural infection. Innate susceptibility or resistance factors in the genetic sense were not sex-linked or related to body vigor, as expressed by unusual fertility or weight. Indeed, so far as these experiments are concerned, all lines of mice tested, save possibly the white-face, were sturdy and normal. The genetic factors are probably multiple, with resistance dominant to susceptibility. Again, the tissues of susceptible mice, not only at the surface but throughout the body, appeared to be more sensitive to *Bacillus enteritidis* than did those of resistant mice, suggesting the general rather than local influence of the inherent factors. Finally, the facts that the white-face line proved relatively susceptible to enteric, respiratory and virus infections, that the Rockefeller Institute susceptible lines were relatively susceptible to enteric and respiratory infections but were resistant to virus infections, and that the Rockefeller Institute resistant lines were resistant to enteric and respiratory infections but were susceptible to virus infections, together with previous observations, indicate that genetic factors segregated by selective and brother-sister inbreeding and concerned with susceptibility or resistance to infection can operate consistently against a number of, but not necessarily all, harmful agents.

AUTHOR'S SUMMARIES.

PHENOMENON OF LOCAL SKIN REACTIVITY TO BACTERIAL FILTRATES IN ITS RELATION TO BACTERIAL HYPERSENSITIVENESS. G. SHWARTZMAN, *J. Exper. Med.* **57**:859, 1933.

The observations reported in this article demonstrate that the intravascular interaction of bacterial and animal protein antigens with homologous antibodies at the site of a tissue made vulnerable by bacterial filtrates induces prompt severe hemorrhagic necrosis in this tissue. In the light of these observations an explanation of the mechanism underlying focal and cutaneous bacterial hypersensitiveness is offered.

AUTHOR'S SUMMARY.

THE IMMUNOLOGICAL RELATION OF POLIOMYELITIS TO LOUPING ILL. F. F. SCHWENTKER, T. M. RIVERS and M. H. FINKELSTEIN, *J. Exper. Med.* **57**:955, 1933.

The results of the work presented in the present paper show that louping ill and poliomyelitis are not closely related immunologically. Although relatively few experiments were performed, the data obtained were sufficiently decisive for our purposes. Certainly nothing was found to indicate that one might be able to immunize human beings against poliomyelitis by the use of the virus of louping ill. In addition to the negative findings, a certain amount of useful information was also secured, namely: Monkeys can be solidly immunized against louping ill by intraperitoneal injections of virus and partially protected by intramuscular administrations of the active agent; during the process of immunization, no signs of involvement of the central nervous system are manifested, and serums from monkeys immunized in the manner described contain antibodies capable of neutralizing the virus.

AUTHORS' SUMMARY.

H AND O TYPHOID AGGLUTINATION. A. D. DULANEY ET AL., *J. Immunol.* **24**: 229 and 235, 1933.

Vaccination against typhoid stimulates the production of H agglutinins to high titers. O agglutinins are also stimulated, but show much lower titers. O agglutination in serum dilutions of 1:100 was demonstrated in 26 per cent of all vaccinated serums and in 11 per cent of a random group of persons. If O agglutination is to have diagnostic value in typhoid fever, higher dilutions of serum than those recommended by Felix (1:100) must be employed. We recommend dilutions of 1:500. In the usual course of typhoid fever both H and O agglutinins are produced. H and O agglutinins to appreciable titer (1:500) are not demonstrated in unvaccinated persons suffering from nontyphoid diseases. O agglutinins seem definitely related to infection. Their demonstration in dilutions of from 1:500 to 1:1,000 is highly suggestive of infection by a member of the typhoid-paratyphoid group, since neither vaccine nor other febrile diseases stimulate to such titers. Typhoid vaccine stimulates the production of H agglutinins to high titers and O agglutinins to low titers (from 1:40 to 1:320). The ordinary Widal test detects only H agglutinins and does not differentiate between infection and vaccination. The use of preserved formaldehydized and alcoholized antigens offers an easy and standardized method of demonstrating H and O agglutinins. H and O agglutination is recommended as a laboratory procedure in typhoid fever, though it could never have the validity of isolation of the causative organism.

AUTHORS' SUMMARIES.

THE INACTIVATION BY HUMAN SERUM OF THE VIRUS OF POLIOMYELITIS. C. W. JUNGEBLUT and E. T. ENGLE, *J. Immunol.* **24**:267, 1933.

The two sets of experiments, taken together, suggest that the power of normal adult human serums to inactivate the poliomyelitis virus in vitro is not a fixed property but may change appreciably in consonance with certain physiologic fluctuations in the endocrine balance of the individual. Thus it becomes increasingly difficult to harmonize the foregoing observations with the orthodox conception, which regards these virucidal substances as the specific reaction product of previous exposure to the virus.

AUTHORS' SUMMARY.

CARBOHYDRATE TYPE-SPECIFIC SUBSTANCES OF PNEUMOCOCCUS. A. WADSWORTH and R. BROWN, *J. Immunol.* **24**:349, 1933.

Type-specific substances of carbohydrate nature obtained from the cells of types I, II and III pneumococci and a nontype-specific substance of carbohydrate nature obtained from an attenuated type I organism were distinct among themselves and also differed from the soluble specific substances of Heidelberger, Avery and others and from the C fraction of Tillett and Francis.

AUTHORS' SUMMARY.

A METHOD FOR SECURING CLEAR SERUMS FROM THE MILK OF COWS AND GOATS. I. C. HALL and R. LEARMONTH, *J. Infect. Dis.* **52**:27, 1933.

In practice, test tubes for the collection of samples of milk are corked in the laboratory, each containing a few cubic centimeters of either chloroform or carbon tetrachloride and a small amount of rennet extract. They are then taken to the dairy and used for the collection of each sample directly from the animal. Each tube is then shaken thoroughly for several minutes to extract the fat. On being returned to the laboratory, all the tubes are placed in the incubator at 37 C. for about an hour to coagulate the casein. They are then centrifugated for fifteen minutes at 2,000 revolutions per minute to separate the milk serum, which will be found in a perfectly clear, deep layer at the top, with a compact curd in the center and the solvent in the bottom. Milk serums collected in this manner may be preserved indefinitely without bacterial growth, owing to the germicidal action

of the solvents, but we have not tested the stability of agglutinins under these conditions. There is no interference with the agglutination test for *Bacterium melitensis* either by inhibition or by false agglutination. If larger numbers of tests are made, it would probably pay to recover the solvents for repeated use by distillation. Carbon disulphide and tetrachlorethane were also tested but were found unsatisfactory, although with both the milk serum separates at the top. But both these solvents definitely inhibit agglutination in the lower dilutions. The use of chloroform or of carbon tetrachloride with rennet in securing clear milk serums from goats and cows for agglutination tests with *Bact. melitensis* is recommended.

FROM AUTHORS' SUMMARY.

PRODUCTION OF AN ANTIPERTUSSIS SERUM OF HIGH TITER. J. H. BAILEY, *J. Infect. Dis.* **52**:97, 1933.

By repeated intraperitoneal injections into cocks of massive doses of a suspension of live, virulent pertussis bacilli, an antipertussis serum of high titer was produced, which did not cause serum sickness, even in large doses and which, in the limited trial afforded it, gave evidence of being of value in the treatment of pertussis in children. No definite statement as to the therapeutic value of this serum may be made until a greater number of patients have been treated.

AUTHOR'S SUMMARY.

AN AGGLUTINATIVE CLASSIFICATION OF THE HEMOLYTIC STREPTOCOCCUS OF SCARLET FEVER. H. J. MUELLER and K. S. KLISE, *J. Infect. Dis.* **52**:139, 1933.

Two hundred and twenty-five strains of hemolytic streptococci from patients with scarlet fever have been examined by agglutination. Two thirds of these fall into six well defined groups; the others remain unclassified. These types include four Griffith types, three of the five Williams types and two groups not included by these workers. These groups are seldom found in normal throats without relation to streptococcic disease. There is evidence that agglutinability is a reasonably constant attribute of hemolytic streptococci, as of other organisms. An agglutinative study of patients with scarlet fever and carriers in isolated epidemics of scarlet fever should be of material assistance in their control.

AUTHORS' SUMMARY.

Tumors

CYTOLOGICAL CHANGES AFTER IRRADIATION OF MALIGNANT GROWTHS. R. J. LUDFORD, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 125.

Cytology of the Transplantable Mammary Carcinoma 27 and the Changes Induced by Irradiation.—A typical cell of this tumor contains a nucleus with one or more plasmosomes and scattered granules of chromatin. In the cytoplasm are filamentous granular mitochondria and Golgi bodies usually grouped together at the side of the nucleus. Secretion is formed in relationship with the Golgi bodies. In the course of degeneration the nucleus shrinks, the chromatin granules run together, and pyknotic nuclei result; the mitochondria break up into granules which become vesicular, and the Golgi bodies disintegrate. The cytologic changes observed after irradiation are as follows: an immediate action on the mitochondria, which become vesicular (forty minutes); inhibition of mitosis (four and one-half hours); growth in the size of the cells, accompanied by an increase in the number of the mitochondria, and enlargement of the Golgi apparatus (twenty-four hours); a return of mitosis, and an indication of intense secretory activity. Considerably enlarged cells are found as late as fourteen days after irradiation, but after three days degenerative changes occur in the enlarged cells to an increasing extent. During degeneration of the large cells the chromatin granules tend to run together

and become converted into an achromatinic substance, and the mitochondria become vesicular and finally fail to stain, while the Golgi bodies are broken up.

Cytology of the Transplantable Mammary Carcinoma 63 and the Changes Induced by Irradiation.—This tumor grows more rapidly than tumor 27, and its cells exhibit no indication of secretory activity. Irradiation results in inhibition of mitosis followed by an outburst of mitotic activity marked by various abnormalities. Enlargement of the cells occurs, but to nothing like the same extent as in tumor 27. The enlarged cells do not secrete, but undergo degeneration. The mitochondria become swollen and vesicular. The Golgi bodies are broken up. These disintegrating cytoplasmic organs are scattered in the cytoplasm.

Cytology of the Transplantable Sarcoma 37 and the Changes Induced by Irradiation.—A typical cell of this tumor has a nucleus with one or more large plasmosomes and scattered granules of chromatin. Its mitochondria are filamentous and granular and tend to collect around the sphere, which is surrounded by a compact group of Golgi bodies. During degeneration the nuclei usually become shrunken and pyknotic, the mitochondria vesicular and the Golgi bodies fragmented. The cytologic changes observed after irradiation are similar to those in tumor 63. There are the same inhibition of mitosis, much the same degree of enlargement and wave of abnormal mitoses and then progressive degeneration. Enlargement of the cells is accompanied by an increase in the number of mitochondria and an enlargement of the Golgi apparatus. During degeneration the disintegrating cytoplasmic organs tend to be collected around the sphere.

Influence of Irradiation on the Reaction of Cells to the Vital Dye Trypan Blue.—There is an increased staining of both normal and malignant cells morphologically altered by irradiation. Irradiated tumor cells do not stain in the same way as their nonmalignant prototypes, nor can segregation of dye be demonstrated immediately after irradiation. Not all strains of transplantable tumor exhibit staining of the enlarged cells following treatment with radium.

Immediate and Late Effects of Irradiation on Different Types of Cells.—The primary effects of irradiation on the colloidal state of protoplasm are probably the same in all cells, as well as the concomitant inhibition of mitosis, but the capacity for recovery, as well as the later changes, differs widely with different types of cells. The greater outburst of mitotic activity after irradiation of the more rapidly growing tumors probably results in larger numbers of nonviable daughter cells, and hence greater cell destruction. Irradiation has no specific action on cancer cells as such.

Direct and Indirect Effects of Irradiation.—The cytologic changes described in this paper are those which occur when malignant growths are irradiated in vivo and left in situ. As Cramer (1932) has demonstrated in another paper in this report, the clinical results of irradiation are not due alone to the direct action of the rays on the malignant cells. Irradiation also induces changes in the stroma, especially in the blood vessels. Thus direct injury to the malignant cells is intensified by interference with their nutrition. The alterations in the cells are therefore the combined result of a direct and an indirect action of the irradiation on the parenchyma of the tumor.

AUTHOR'S SUMMARY.

THE DIFFERENTIAL REACTION TO TRYPAN BLUE OF NORMAL AND MALIGNANT CELLS IN VITRO. R. J. LUDFORD, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 169.

Mouse Fibroblasts and Sarcoma Cells.—Fibroblasts of embryonic and adult tissues, as well as those of reaction tissues, segregate trypan blue in vitro in the form of droplets. Unfavorable conditions of growth interfere with segregation. Cell death results in diffuse passive coloration. In cultures of mouse sarcomas the macrophages stain intensely, but not the malignant cells. Although these sarcoma cells do not segregate dye as do fibroblasts, staining occurs in some degenerating cells, and under unfavorable conditions of growth. Sarcoma cells,

like fibroblasts, exhibit phagocytic activity. This affords clear evidence that segregation and phagocytosis are two different processes. Dead sarcoma cells show a diffuse passive coloration.

Mammary Gland Cells and Mammary Carcinoma Cells of the Mouse.—Mammary gland cells are usually intensely stained in vitro. When growing as a sheet, the cells become filled with fine droplets of the dye. The carcinoma cells in cultures of tumors 27, 63 and 206 do not segregate dye, although they may exhibit considerable phagocytic activity. Vital staining with trypan blue affords a good method for distinguishing between carcinoma cells and the macrophages which wander out from explants, since the latter stain intensely and the carcinoma cells do not.

Mouse Epidermal Cells and Carcinoma Cells of Epidermal Origin.—In cultures of embryonic mouse skin growing as a sheet on the surface of a plasma clot the epidermal cells segregate dye as fine droplets, and occasionally come to contain large colored inclusions, probably passively colored keratohyalin. The malignant cells of the transplantable tumor 2146, which originates as a tar carcinoma, do not segregate dye, although macrophages of the same tumor stain intensely.

Rat Fibroblasts and Sarcoma Cells.—Rat fibroblasts segregate trypan blue in vitro in the same manner as those of the mouse. In cultures of the Jensen rat sarcoma and of sarcoma 41, the macrophage type of cell is intensely stained. The sarcoma cells sometimes segregate dye, and in some cultures of the Jensen sarcoma there has been observed a considerable amount of segregation. This has occurred when the tumor was growing badly in vivo, and it is suggested that there may be some relation between segregation and the state of activity of the cells. The cells of both the Jensen sarcoma and sarcoma 41 are actively phagocytic.

Fibroblasts and Cells of the Filtrable Tumors of the Fowl.—Fibroblasts in cultures of chick embryo heart react to trypan blue in the same manner as those of the mouse and rat. Macrophages which wander out from the explants in cultures of the filtrable tumors of the fowl stain intensely with trypan blue. They are not regarded as the malignant cells of these tumors. In the cultures there is another type of cell which rarely contains much dye and which is regarded as the malignant cell. Frequently these cells do not wander out from the explants, and are therefore best studied by teasing, or by cutting serial sections. The cells of the endothelioma MH2 are actively phagocytic.

Cancer cells, when growing in vitro, do not segregate trypan blue in the same way as their nonmalignant prototypes.

AUTHOR'S SUMMARY.

VITAL STAINING OF FOWL TUMOURS. L. FOULDS, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 191.

It is shown that the parenchyma cells of six varieties of filtrable tumor of the fowl rarely segregate trypan blue under conditions which lead to its active segregation by histiocytes, fibroblasts and other normal cells. Under certain conditions the cells of the endothelioma Mill Hill 2 are strongly phagocytic and may ingest large amounts of granular dye. Similar activity was not observed in tumors of other types. The absence of segregation is common to all the tumors examined, and is independent of the cell type, rate of growth or degree of differentiation. The fibrosarcomas are almost benign tumors which form abundant collagen and varying amounts of elastic tissue, and allow the survival of the host for many weeks or months. At the other extreme stands the Rous sarcoma 1, which is very cellular, forms little collagen (which is prone to degeneration) and kills the fowl, usually in three weeks. There is no constant difference in staining between these strongly contrasted types. The slow growth of the fibrosarcomas allows intense staining of the fowls and, during the time required, the tumors increase little in size. Here there can be no question, as may be raised for the sarcomas, whether the administration of dye can keep pace with the increasing bulk of the tumor. The deposition of dye at the periphery of the cytoplasm and in the intercellular matrix of these growths, which I interpret as an adsorption to fibrils, demonstrates

the access of dye to the surface of cells in the densest parts of the growths, although the cells fail to segregate it. Each of the tumors contains cells with dye, usually small in amount. It is difficult to determine the exact proportion of cells which stain on account of the uncertainty in the differentiation of tumor cells from stroma cells. It is clear, however, that they form only a minority. The observations here described correspond closely to those of Ludford (1929) and others on tumors of mice and to observations on the same tumors cultivated in vitro (Ludford, 1932). In vivo and in vitro, the parenchyma cells of tumors of fowls differ from their normal prototypes in their reaction to trypan blue, but closely resemble the cells of tumors of mice. Vital staining with trypan blue, therefore, reveals no difference between avian and mammalian neoplasms.

AUTHOR'S SUMMARY.

RETROPERITONEAL GANGLIONEUROMA. N. HORTOLOMEI, G. CHIPAIL and M. FERDMANN, *Ann. d'anat. path.* 9:585, 1932.

A retroperitoneal ganglioneuroma is described, composed of nerve fibers and sympathetic ganglion cells. The subject is discussed, especially the work of Masson. The tumors are rare; they are benign, and they are derived from the sympathetic nervous system and its derivatives (suprarenal medulla).

PERRY J. MELNICK.

THE HISTOLOGY OF KAPOSI'S SARCOMATOSIS. H. HAMDI and HASSAN RESAT, *Ann. d'anat. path.* 9:593, 1932.

The authors studied three cases of Kaposi's sarcomatosis. These multiple growths of the skin are vascular tumors with marked perivascular proliferation of cells. The early stages appear like angiofibromas. Later there is a marked increase in vascularity, the new-formed vessels varying in caliber from the diameter of a red cell to the size of an arteriole. The proliferating perivascular cells are fusiform, and in the older lesions they are markedly increased in number and are round to oval. The lymphatics are compressed and dilated. Each lesion is entirely independent of the others. The variations in the histologic picture have resulted in different opinions among various authors.

PERRY J. MELNICK.

MYELOMA. N. BALAN and L. BALLIF, *Ann. d'anat. path.* 9:873, 1932.

The authors give a general discussion of myeloma and present a case of plasmacytoma, which is interesting because large numbers of megakaryocytes and eosinophils were found in some of the nodes.

PERRY J. MELNICK.

CONGENITAL EPULIS (ITS HISTOGENESIS). P. MOULONGUET and GENEVIEVE DELAMBERT, *Ann. d'anat. path.* 9:887, 1932.

In studying thirteen cases of the rare congenital epulis, the authors came to the conclusion that it is a form of benign adamantinoma, a sort of embryonic misplacement of nests of ameloblasts. The spongy cells surrounding the nests of ameloblasts are interpreted as degenerated groups of these cells, similar to the central degenerated spongy cells of ordinary adamantinomas, but having an opposite polarity or distribution.

PERRY J. MELNICK.

ARACHNOIDAL ANGIOMAS AND TELANGIECTASIAS. L. CORNIL and H. MOSINGER, *Ann. d'anat. path.* 9:955, 1932.

In a thorough review of arachnoidal telangiectasias and angiomas, the authors come to the following general conclusions: Telangiectasias (venous capillary or arterial) are of congenital or acquired origin. In the latter case, traumatic or inflammatory causes are important. In a number of cases angiomas are engrafted on preexisting telangiectasias of an inflammatory nature, i. e., a capillary proliferation of a reactive nature which becomes transformed into a hyperplastic tumor-like process.

PERRY J. MELNICK.

Medicolegal Pathology

AN OUTBREAK OF THALLICOSIS. J. C. MUNCH, H. M. GINSBURG and C. E. NIXON, J. A. M. A. **100**:1315, 1933.

Of thirty persons who ate tortillas containing grain with about 1 per cent of thallium sulphate, symptoms of intoxication developed in twenty within from one to three days, six of whom died. The symptoms were abdominal colic, nausea, vomiting and diarrhea or constipation, stomatitis, alopecia, peripheral neuritis, strabismus and other indications of cerebral involvement. Postmortem examination showed grossly alopecia, stomatitis, yellow liver and pulmonary and leptomeningeal congestion. The microscopic examination showed fatty infiltration and central necrosis in the liver, diffuse nephritis, gastro-enteritis, degeneration and hemorrhages in the suprarenal medulla and degeneration of the nerve cells. Thallium was demonstrated in the kidneys, liver, lungs and spleen.

BLOOD GROUPING IN QUESTIONS OF BLOOD RELATIONSHIP. A. S. WIENER, J. Immunol. **24**:443, 1933.

The chances of proving nonpaternity, when the type of the falsely accused man is known, were calculated. In New York City the average chances of proving nonpaternity by means of all four agglutinogens, A, B, M and N, are approximately one in three. A man of type A++ has less than one chance in ten to prove his innocence, and a man of type B++ has only one chance in seven. Men of the remaining ten types, however, have chances ranging from one in four (O++) up to two in three (AB-+). The chances of detecting interchange of infants in hospitals by means of the agglutinogens, A, B and M and N, are seven in ten.

AUTHOR'S SUMMARY.

EMISSION SPECTROGRAPHY IN DETECTION OF METALS IN TISSUES. W. GERLACH and K. RUTHARDT, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:151, 1932.

With the spectrographic method, sensitive elements, such as gold, silver, copper, manganese, lead, thallium and mercury, can be easily demonstrated and their presence photographically recorded. The technical procedures do not require more time than a qualitative chemical analysis.

E. L. MILOSLAVICH.

THE CHARACTERISTICS OF BLOOD GROUPS M AND N. W. CROME, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:316, 1933.

Of 1,300 persons, 49 per cent belonged to group MN; 32.5 per cent to group M, and 18.5 per cent to group N. These groups act as mendelian genes as determined in a study of 22 families with 50 children. Three pairs of monozygotic twins were found to belong to the same blood group. The method requires careful controls and an experienced serologist. It is a valuable addition to our methods of studying paternity and maternity relations.

JACOB KLEIN.

THE USE OF NITRIC OXIDE GAS IN THE DIAGNOSIS OF AIR EMBOLISM AND DEMONSTRATION OF RESPIRATORY ACTIVITY IN THE NEW-BORN. DYREN-FURTH, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:341, 1933.

Two analytic gas methods are described for determining the presence of oxygen in the given tissues (lungs). The one consists of placing the previously dried and hardened tissue in a cylinder with a measured amount of nitrogen. The chamber is then heated, thus liberating oxygen from the tissues. This mingles with the nitrogen in the cylinder, the amount of oxygen being determined by buret titration with alkaline pyrogallol solution. The other method exposes the tissues to nitric oxide gas. This forms nitrogen dioxide with the liberated oxygen. The nitrogen dioxide is mixed with potassium iodide solution, thus liberating free iodine

which is titrated with tenth-normal thiosulphate solution, 1 cc. of which equals 1.14 cc. of oxygen. In this report there is no particular application of the method to air embolism: the emphasis is placed on the technic.

JACOB KLEIN.

STRANGULATION WITHOUT LOCAL SIGNS OF TRAUMA. (THE MEDICOLEGAL SIGNIFICANCE OF HERING'S CAROTID-SINUS REFLEX.) A. ESSER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 20:361, 1933.

A girl was found dead with a loop about her neck under conditions which indicated suicide. However, her lover confessed that he had choked her and then arranged the loop. The unusual feature was the lack of local changes ordinarily associated with choking. There is a detailed discussion of Hering's reflex as a cause of sudden death. It has been demonstrated experimentally by Hering that pressure on the carotid, particularly over the carotid sinus, causes a lowering of the pulse rate and blood pressure. In certain persons unconsciousness may result. This possibility should be considered in cases of death from strangulation.

JACOB KLEIN.

HISTOLOGIC STUDIES OF LUNG TISSUE IN THE NEW-BORN AS A TEST OF VIABILITY. K. BÖHMER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 20:391, 1933.

Tests for the demonstration of previous respiration in new-born infants are in many respects inadequate. The author studied the elastic tissue in a series of new-born infants with Weigert's stain, where the blue color is induced by the action of oxygen on the iron chloride in the stain. The author concludes that this method is an important aid in determining whether or not respiration of air has occurred in the new-born. There was a distinct difference noted in the staining of the elastic tissues in atelectatic lungs and those which had functioned. In the latter instance the oxygen in the tissues oxidizes the iron in Weigert's stain with resulting dark blue color in the elastic tissue.

JACOB KLEIN.

THE BRONCHIAL TREE IN THE DECOMPOSING LUNG OF THE NEW-BORN. A. FOERSTER, *Deutsche Ztschr. f. d. gerichtl. Med.* 20:420, 1933.

The determination of the occurrence of spontaneous respiration is difficult in decomposing pulmonary tissue of the new-born. By using Weigert's elastic tissue stain the bronchial tree may be readily demonstrated, even when other tissue elements are disintegrated. On the basis of the examination of sixty lungs of new-born infants and from four medicolegal cases, the author concludes that the method satisfactorily demonstrates the bronchial tree, which is fully expanded when respiration has taken place. However, the diagnosis must not be made on one section, but should include a study of the lung from the hilus to the periphery.

JACOB KLEIN.

CHANGES IN THE RESPIRATORY ORGANS FROM SUDDEN EXPOSURE TO HIGH TEMPERATURES. A. FOERSTER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 20:445, 1933.

Peculiar changes occurred in the bronchial mucosa in two cases in which the lungs were exposed to heat by aspiration. The epithelium of the bronchial mucosa became markedly elongated and arranged in "palisade" formation. The same changes were demonstrated in vital and postmortem experiments on dogs.

JACOB KLEIN.

SPONTANEOUS OR TRAUMATIC RUPTURE OF THE AORTA. A. ESSER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 21:27, 1933.

A man, while sitting on a porch, fell two stories to the ground and immediately died. There were found hemopericardium, rupture of the pericardium, arterio-

sclerosis of the coronaries and a complete tear in the aorta, 2.5 cm. below the arch. It was concluded that the site and nature of the rupture proved it to be due to trauma sustained in the fall.

JACOB KLEIN.

FAT EMBOLISM OF THE LUNGS OF A BURNT HUMAN BODY. R. KOCKEL, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **21**:112, 1933.

In a burnt motor truck was found on the driver's seat a partially incinerated human body. The question arose whether this was the body of the driver. It was established that the body was that of a rather young man of slender build with reddish hair. The heart blood did not contain any carbon monoxide. There was no soot in the respiratory passages, and the lungs showed well marked fat embolism. From these observations it was concluded that the body was not that of the driver, that it had been burnt after death, and that the fat embolism in the lungs was the result of injuries received during life. The subsequent developments in the case substantiated these conclusions. The driver was found to be alive. The motive of the crime was to obtain certain insurance money.

VITAL REACTIONS OF BRONCHIAL ELASTIC FIBERS. A. FOERSTER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **21**:146, 1933.

The longitudinal elastic fibers of the bronchi were studied microscopically in animals which had been exposed to heat. The elastic fibers (Mallory stain) were markedly distorted into a characteristic network. Such changes were not seen in animals exposed to heat post mortem.

JACOB KLEIN.

INTRAVITAL ENCLOSURE OF AIR BUBBLES IN CLOTS. K. WALCHER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **21**:146, 1933.

In a fatal case of pneumohemothorax from a bullet wound through both upper pulmonary lobes, the superior vena cava, the bronchi and descending aorta, air bubbles enclosed in fibrin were found in the blood clots. The presence of air bubbles indicates that the pneumohemothorax occurred during life.

JACOB KLEIN.

SUDDEN DEATH FROM A PEDUNCULATED LIPOMA OF THE ESOPHAGUS. G. WEYRICH, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **21**:164, 1933.

A 58 year old man, who had died suddenly without any previous illness, was found to have a pedunculated lipoma, 9.5 cm. long, attached to the anterior wall of the esophagus. The free end of the tumor had obstructed the larynx and caused death by suffocation.

JACOB KLEIN.

BLOOD GROUP DETERMINATIONS ON THE CADAVER. GEORG STRASSMANN, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **21**:168, 1933.

In the putrefying cadaver when serum is not otherwise obtainable, blood grouping may be successfully carried out on pericardial fluid, pleural and abdominal transudate, hydrocele fluid, serum from blisters on the skin, contents of the seminal vesicles, vaginal secretions and saliva.

JACOB KLEIN.

CONTRECOUP INJURIES OF THE BRAIN. E. HELLENTHAL, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **21**:250, 1933.

Contrecoup injuries result from the action of blunt force on the skull, and arise from direct extension of the impulse in the brain, with slight lateral spread. On reaching a ventricle a traumatic impulse is diffused in all directions, the lateral impulse being exaggerated. The fluid in the subarachnoid space acts as a pro-

tection to the brain. The parts of the brain most frequently involved are the lower surfaces and tip of the frontal and temporal lobes, chiefly where there is transition from the base, due to an absence of protective liquid at these places. Several traumatic impulses may arouse waves which meet at a point in the brain and cause the so-called central rupture of the brain.

JACOB KLEIN.

CHLORATE POISONING. W. BOSÆUS, *Upsala läkaref. förh.* **37**:341, 1932.

Two new cases of chlorate poisoning are described, one suicidal and one accidental. A fundamental difference between poisoning from sodium chlorate and that from potassium chlorate does not seem to exist. In the early stages of the poisoning, hemoglobin may be set free in the form of yellow granules; there may be signs of regeneration of red cells with erythroblasts and red cells with basophil and polychromatophil granules. At the same time, there may be leukocytosis with an increase in the percentage of polymorphonuclear nuclei and a decrease of the small lymphocytes. Fat deposits may appear in leukocytes. In the epithelial cells of the renal tubules may be found drops of hemoglobin; in a protracted case, casts of hemoglobin in the collecting tubules appeared to have set up foreign body reactions in the surrounding tissue. In two of the cases described by the author, fat embolism and extensive fat infiltration were observed in different tissues and organs. The fat embolism is regarded as the result of lipemia, because in both cases the fat drops contained lipid substances. Pure fat emboli were scarce. In one of these cases thrombi had formed in the liver, consisting of a mixture of fat drops and blood detritus. These thrombi were found especially about small foci of necrosis due to capillary obstruction. It appears that when ulceration in the digestive tract develops in chlorate poisoning, the ulcerative lesions are of the same type as those observed in other conditions with severe blood disintegration.

FROM AUTHOR'S SUMMARY.

Technical

IMMEDIATE TYPING OF PNEUMOCOCCI IN SPUTUM. A. R. SABIN, *J. A. M. A.* **100**:1584, 1933.

The method is based on the change that develops in the peripheral zones of the pneumococcus when it is placed in specific immune serum. This phenomenon was described first by Neufeld. Sabin places two small flecks of sputum on the same cover slip and covers one with immune rabbit serum, type 1, and the other with immune rabbit serum, type 2. A loopful of standard alkaline, methylthionine chloride, U. S. P. (methylene blue), is added in each case. In the type-specific mixtures the pneumococci, stained blue, are surrounded by a refractile substance resembling ground glass.

METHOD FOR MOUNTING GROSS PREPARATIONS IN A MUSEUM. S. MAHRBURG, *Virchows Arch. f. path. Anat.* **289**:312, 1933.

The author describes a simple and inexpensive method of mounting gross specimens on a glass plate in glycerin jelly. After the jelly has set it is rendered insoluble by treatment with solution of formaldehyde, and the reverse side of the specimen is painted with tar, obviating the use of any sort of container.

O. T. SCHULTZ.

Society Transactions

PATHOLOGICAL SOCIETY OF EASTERN NEW YORK

ARTHUR W. WRIGHT, *Secretary*

Regular Meeting, Feb. 3, 1933

STEPHEN H. CURTIS, *Presiding*

GANGLIONEUROMA OF THE LEFT RETROPERITONEAL SYMPATHETIC CHAIN. J. SCHLEIFSTEIN.

Ganglioneuroma is still sufficiently rare to warrant the recording of new cases. This case occurred in a girl, single, 18 years of age. With the exception of the usual children's diseases and a tonsillectomy in 1930, she was healthy, doing all kinds of farm labor such as running a tractor and plowing. Three years ago, while stanchioning the cows, she was bunted in the lower middle portion of the abdomen. She was not disabled, but suffered some discomfort for a few days. In January, 1930, she hurt her back, but was not confined to bed.

About a month later she began to have pain in the lower lumbar region, which lasted for a few days. Subsequently, similar attacks occurred. At times the pain traveled down the legs, but was always present in the back and the left side of the abdomen. In the spring of 1931 she weighed 125 pounds (56.7 Kg.); on examination, 112 pounds (50.8 Kg.). Examination of the chest showed no abnormalities; the menstrual history was essentially normal, and significant neurologic symptoms were absent. No findings of diagnostic importance were obtained by laboratory tests. Physical examination showed a large mass on the left side of the abdomen in the lumbar region, which gave no pain on palpation. It did not seem to extend into the pelvis or protrude beyond the costal border, but reached to the midline of the abdomen. An operation was performed, and a large retroperitoneal tumor was found. The posterior peritoneal layer was incised, and an attempt was made to enucleate it. Since the tumor could not be defined and was firmly affixed, removal was not attempted. It extended to the pelvis and as far as the kidney, but did not include the latter. A few sections were taken for biopsy, and the abdomen was closed. The patient remained in the hospital for five days, made an uneventful recovery from the immediate operation, and was allowed to go home. The subsequent history of the case indicated that the patient was apparently in good health eighteen months after the operation.

Histologic Examination.—Three small sections of tissue were received, each about the size of an almond. They were grayish pink and somewhat soft.

The tumor consisted essentially of two main elements: bundles of nerve fibers, chiefly nonmedullated, and large ganglion cells. Numerous compact bundles of nerve fibers extended in various directions. Many unipolar and bipolar ganglion cells were observed which approached the form of large round cells and tended to occur in foci. Various stages of degeneration were noted in several of them. The supporting connective tissue appeared somewhat myxomatous and contained small foci of lymphocytes. The tumor was a typical ganglioneuroma, arising probably from the left retroperitoneal sympathetic chain. The kidney and suprarenal appeared to be free.

FIBROMA OF THE UMBILICUS. J. SCHLEIFSTEIN.

A girl, 16 years of age, was thought to have an umbilical hernia. The umbilicus with the surrounding tissue was removed at operation and submitted for histologic examination.

Histologic Examination.—An umbilicus, quite firm, about the size of an almond and raised above the surrounding skin, was received. Cut section showed a grayish-white surface composed principally of fibrous tissue. The tumor appears to consist chiefly of fibrous connective tissue containing numerous sweat glands. The findings seem to correspond closely to those described by Cullen (*Embryology, Anatomy, and Diseases of the Umbilicus Together With Diseases of the Urachus*, Philadelphia, W. B. Saunders Company, 1916, p. 537) as characteristic of fibroma of the umbilicus. This specimen is of interest because of the infrequent occurrence of the condition.

SARCOMA OF THE STOMACH. J. SCHLEIFSTEIN.

Sarcoma of the stomach is still sufficiently rare to be placed on record. The patient was a married woman, 46 years of age. The only history available was that a laparotomy was done. A tumor, the size of a walnut, was found on the greater curvature of the stomach and removed. The surgeon did not consider it malignant.

Histologic Examination.—The gross specimen was a tumor nodule, about the size of a walnut, circumscribed and firm. In section it did not look unlike a myoma. It consisted essentially of interlacing bundles of highly anaplastic cells and contained numerous mitotic figures and some giant cells. It appeared to be growing rapidly, and in some parts of the section it had invaded the blood vessels. The histologic structure was that of a myosarcoma. This type of tumor is malignant and offers a poor prognosis, the average life of a patient being a little over three years. The tumor tends to produce huge metastases to the liver.

HODGKIN'S DISEASE: A REPORT OF THE POSTMORTEM STUDY OF TWO CASES. ARTHUR W. WRIGHT.

Theories concerning the etiology of Hodgkin's disease are of great interest at the present time. Among the most significant recent studies are those of L'Esperance, who, with Ewing, considers the disease to be a form of tuberculosis probably due to infection with the avian tubercle bacillus, and of Medlar, who believes the disease to be a malignant tumor originating from the megakaryocyte of the bone marrow.

Two cases of Hodgkin's disease which came to necropsy are reported. The first was that of a 14 year old boy who suffered from indigestion, nausea and general weakness and who had a constant though fluctuating fever. The superficial lymph nodes were not palpable, but the spleen was enlarged. Marked anemia and leukopenia were present. Roentgen examination revealed a large mediastinal mass. The condition was diagnosed clinically as miliary tuberculosis. Death occurred about three months after the onset of the disease.

Post mortem there were found: enlarged, matted, markedly necrotic retroperitoneal and mediastinal lymph nodes; marked splenomegaly with suet-like foci of necrosis; a large liver with multiple foci of necrosis, and a hyperplastic bone marrow. The microscopic changes were typical of Hodgkin's disease except for very large foci of acute necrosis of the spleen, liver and lymph nodes and for the presence in all of these organs of abundant phagocytic endothelial leukocytes filled with red blood cells. These cells represent active destruction of blood. So-called Sternberg or Dorothy Reed cells were present in all of the lesions. Fibrosis was only moderate. The bone marrow was extensively involved. No tubercle bacilli could be demonstrated.

The second case, that of a 30 year old colored man, was less acute and was characterized by nausea, indigestion, progressive loss of weight, splenomegaly, ascites, hypertrophy of all the superficial lymph nodes, as well as those of the mediastinum, and fever of the Pel-Ebstein type. Profound progressive anemia and leukopenia were present. In blood films phagocytic cells containing Leishman-Donovan-like bodies were said to have been found, and a clinical diagnosis of kala-azar was made. Death occurred about a year after the onset of the disease.

Necropsy disclosed the characteristic pathologic changes of Hodgkin's disease affecting the spleen, liver, bone marrow and practically every lymph node of the body. Histologically the lesions were older than were those in the first case. Necrosis was less extensive and hyaline fibrosis more marked. There was no evidence of kala-azar. Tubercle bacilli were not found in any of the sections.

These cases, incorrectly diagnosed clinically, are presented to call attention to the importance of adequate and careful clinical and laboratory studies on all obscure chronic diseases with lymphadenopathy, either superficial or mediastinal or both, splenomegaly and fever. Histologically the disease presents the characteristics of an infection rather than those of a malignant tumor.

METASTASIZING LEIOMYOSARCOMA OF THE UTERUS. M. CRISCITIELLO, JR.

A colored woman, 64 years of age, was admitted to the hospital complaining of indefinite abdominal pains and vaginal bleeding. The family history and the past history were of no significance. The patient began to menstruate at the age of 12, and up to the onset of the present illness had had no noteworthy irregularities. She was married at the age of 40, and her husband died ten years later. There were no pregnancies.

About ten years before admission the patient noticed abnormal vaginal bleeding, which manifested itself first in the form of menorrhagia and later metrorrhagia. She paid little attention to these irregularities until four weeks before admission to the hospital, when she bled rather profusely for twelve days. This bleeding was accompanied by slight abdominal pain. After several days of freedom from flow she again began to bleed and had been flowing intermittently until admitted to the hospital. There was a foul odor to the discharge. On admission the patient complained of weakness and loss of appetite.

She was a rather obese colored woman. The chest was normal in contour. The heart showed no enlargement. A loud systolic murmur at the apex, transmitted to the left axilla, and a presystolic murmur, heard best in the second left interspace, were present. The blood pressure was 174 systolic and 80 diastolic. The lungs were resonant except for moist râles over the bases. An irregular, hard, nodular mass filled the lower part of the abdomen. Vaginal examination was unsatisfactory because of the nulliparous outlet. There was slight edema of both ankles.

The red blood cells numbered 2,321,000; the hemoglobin was 35 per cent; the white blood cells numbered 9,200, with 70 per cent polymorphonuclears and 30 per cent lymphocytes. The red cells showed moderate achromia and marked anisocytosis, poikilocytosis and polychromatophilia. The Wassermann reaction of the blood was negative. The urine contained a trace of albumin but no sugar. Much pus was present in the sediment.

A provisional diagnosis of papillary cystadenoma of the ovary or multiple leiomyomas of the uterus was made.

An operation, though necessary, could not be performed because of the poor condition of the patient. Two blood transfusions failed to cause improvement. The patient continued to bleed, and her general condition grew worse. On April 12 she had a profuse hemorrhage following which she died rather suddenly.

At necropsy the most important finding was a large lobulated tumor which filled the lower portion of the abdominal cavity and the pelvis. On removal this mass weighed 4.8 Kg. and was found to consist of the uterus from which sprang multiple smooth, spherical, encapsulated tumors which originated within the myometrium. Most of these tumors were typical leiomyomas. One of them had undergone calcification and could not be cut through. Another, however, was soft and friable, its cut surface resembling brain tissue. This tumor, although partially encapsulated, had broken through the endometrium and had filled the distorted uterine cavity with a soft, spongy, polypoid growth which was necrotic and sloughing. It was obviously malignant.

The ascending colon and several loops of small intestine were adherent to the pelvic mass. The liver, spleen and kidneys showed nothing of note. Throughout

both lungs, especially at the bases, there were many small, roughly spherical tumor masses, varying in diameter from 1 to about 4 or 5 cm. These masses were clearly outlined and white, and on section were found to consist of homogeneous, friable, neoplastic tissue.

The heart was slightly enlarged. In the wall of the right ventricle there was a small metastatic tumor nodule, 1 cm. in diameter. This nodule extended into the right ventricle. Another similar but smaller nodule was enmeshed in the chordae tendineae.

Microscopic examination of the friable, degenerated uterine mass showed atypical, undifferentiated, neoplastic cells which varied morphologically, some being spindle-shaped and others round. Many multinucleated cells and abundant mitotic figures were present. Sections from the pulmonary and myocardial metastases presented the same histologic picture as that of the primary tumor. The tumor was considered to be a rapidly growing leiomyosarcoma of the uterus with metastases to the lungs and the myocardium. The neoplasm apparently originated as the result of malignant transformation of a benign leiomyoma.

PERIARTERITIS NODOSA. V. C. JACOBSEN.

A Negro, 49 years of age, complained of gastric distress and weakness associated with diarrhea, fever and a slow pulse. Physical examination showed midabdominal tenderness, a large heart and sclerosis of the superficial arteries. The Wassermann reaction of the blood was strongly positive. The white cell count varied between 11,000 and 20,000. Diagnoses of acute gastro-enteritis and syphilis were made. The symptoms disappeared shortly, but the fever persisted.

One month later he complained of constant pain in the umbilical region and the loss of 60 pounds (27.2 Kg.) during the preceding three months. The skin was dry and the throat reddened; the cervical, axillary and inguinal glands were enlarged. The white cell count dropped to 9,400. There was a low grade fever.

Five months later he complained of umbilical and retrosternal pain associated with vomiting, dyspnea, weakness and some impairment of vision and hearing on the right side. The hemoglobin was 60 per cent. The white cell count was 5,500. The nonprotein nitrogen content of the blood, which six months previously was normal, now rose to 208 mg. The blood pressure, which was previously slightly elevated, rose to 192 systolic and 140 diastolic. An electrocardiogram showed left axis deviation and complete branch block.

At autopsy the heart was enlarged and the coronary arteries were thick, tortuous and beaded. The beadlike structures occurred along the sides of the arteries and in some instances completely encircled the vessels. These structures varied from 2 to 5 mm. in diameter and were pearly white. They were most numerous along the posterior branches of the right coronary artery.

The kidneys were of normal size, but showed extensive arteriosclerotic changes. Section revealed small, white, beadlike structures, 2 mm. in diameter, along the larger vessels in the medulla. The left testicle showed early infarction with thrombosis of the spermatic artery.

Microscopic study showed all stages of so-called periarteritis nodosa. The early stage was characterized by fragmenting of the muscle cells in the media and their replacement by a fibrinous exudate. There occurred invasion of the media and adventitia by lymphocytes, polymorphonuclear neutrophils and plasma cells. Edema of the perivascular connective tissue was often present.

Other stages showed an invasion of the fibrinous exudate by fibroblasts and young blood vessels which finally resulted in scar formation or hyalinization. The intima in many instances showed endothelial proliferation. The elastica interna and externa became fragmented at the site of the medial lesion.

Similar vascular changes were found in the arcuate arteries of the kidneys. A proliferative type of intracapillary glomerulonephritis was present. The spermatic arteries were much affected and often thrombosed. Many other small and medium-sized arteries throughout the body showed the changes described. Additional

lesions were: acute lobar pneumonia, generalized arteriosclerosis, central zone necrosis of the liver, chronic pyelitis, chronic prostatitis and chronic fibrous orchitis.

A CASE OF CYSTIC DEGENERATION OF A LARGE MYOMA SIMULATING PREGNANCY. ELLIS KELLERT.

A woman, aged 45, entered the hospital complaining of vaginal bleeding. The last pregnancy occurred twenty-three years before. There had been one miscarriage. The menses were regular until the onset of the present illness, which began four days before admission with vaginal bleeding associated with pain in the lower part of the back and abdomen. The patient stated that the pains were much like those occurring during labor. No chills, fever or gastro-intestinal disturbances were experienced.

The patient was obese. The only significant physical finding was an enlarged uterus with moderate tenderness in the lower portion of the abdomen. The urine contained red blood cells, but was otherwise normal. The blood count was normal, but there were moderate achromia, anisocytosis and poikilocytosis.



Leiomyoma of the uterus undergoing cystic change. Clinically, the symmetrical enlargement of the uterus simulated a normal pregnancy.

A curettage was performed and greenish fluid obtained, but nothing of diagnostic importance was seen. Several days later the abdomen was opened, and a soft, symmetrically enlarged uterus was found. On palpation no intramural masses were detected. The enlarged organ so closely simulated a pregnant uterus that it was not removed. After this operation an Aschheim-Zondek test for pregnancy was done and found negative.

The patient left the hospital, but the symptoms continued. She returned at the end of three months, and a hysterectomy was performed.

The gross specimen consisted of a uterus with both tubes and the left ovary attached. The uterus measured 12 by 10 by 9 cm. The cervix was not present. The serosa was markedly roughened and injected. The lower half of the uterus was wider and thicker than the fundus, but readily compressible. On section, the uterine wall was represented by a thin layer of smooth muscle within which was a thin layer of myomatous tissue enclosing a cavity, 9 cm. in diameter. This cavity was filled with turbid, greenish-yellow fluid and was divided into several compartments by broad thin bands of myomatous tissue. Masses of fibrin were present in the lower half of the cyst. The endometrial cavity was small and compressed toward the fundus. The endometrium appeared normal. The tubes were not

enlarged or thickened; the serous surfaces were smooth and studded by many minute grayish cysts. The ovary was atrophic.

The fluid from the myoma had a specific gravity of 1.025. No seromucin was present. Smears of the centrifugated sediment showed red blood cells, few leukocytes and no bacteria. Cultures were sterile.

The diagnosis was: a large leiomyoma of the uterus undergoing complete cystic degeneration, hypertrophy of the uterus, glandular hyperplasia of the endometrium and atrophy of the ovary; the fallopian tubes were normal.

AN UNUSUAL POLYP OF THE CERVIX. ELLIS KELLERT.

A woman, aged 56, entered the hospital on May 10, 1931, complaining of bleeding from a tumor mass in the vagina. She had had seven children, five of whom were living and well. There had also been one miscarriage. For many years she had



Large polyp of the cervix which on vaginal examination simulated the fingers of a fetus.

been conscious of a mass in the vagina. Two days before admission she noticed bleeding and conferred with a midwife, who after examination said that she would be all right later. The bleeding became more pronounced, and the patient called a physician. He made a vaginal digital examination and thought that he palpated the fingers of a fetus. She was brought to the hospital and the vagina was examined by means of a speculum. A large cervical polyp was found and removed. It was attached to the left side of the cervix by means of a short narrow pedicle. A smaller polyp was attached to the left side of the cervical canal.

The gross specimen consisted of a skin-covered polypoid mass measuring 7 by 7 by 4 cm. At the narrow end was a cauterized area, 1.5 cm. in diameter. The external surface was thickened, ridged and rough, and had a warty, spinous appearance. Numerous tapering, finger-like projections were attached to the surface. They were about the size of infant fingers and arranged roughly in two rows, one at the larger and broader end of the mass and the other near the narrow attached end. On section, soft, grayish, fibrous tissue was found.

The diagnosis was: a large papilloma or polyp of the cervix having unusual surface configuration and finger-like projections.

A FATAL CASE OF ARGYRIA. G. H. KLINCK, JR.

At a previous meeting of the society (Klinck, G. H., Jr.: *ARCH. PATH.* **15**: 751, 1933), a case of profound argyria was presented in which silver was demonstrated in sections of the skin. A large bladder stone (575 Gm.) from the same patient contained no silver. The patient was discharged after a prolonged convalescence and returned to the hospital two weeks later, very dehydrated. She died in uremia.

Autopsy showed the cutaneous pigmentation previously reported. The heart muscle was atrophic and dark purplish gray, and minute vegetations were present on the mitral valve. Microscopically the stroma showed many silver granules unevenly distributed, often in clumps about small vessels, and a fine deposit rather generalized in the connective tissues. The vegetations contained no silver.

The lungs showed hypostatic pneumonia. Microscopic sections revealed small deposits of silver in the walls of some of the pulmonary veins. The spleen weighed 35 Gm. It showed adhesive capsulitis with silver granules fairly numerous in the thickened capsule but infrequent in the pulp. The liver capsule was grayish. Numerous small foci of necrosis were present. The walls of the veins were gray, owing to heavy deposits of silver granules. The Kupffer cells contained no pigment. The gallbladder contained silver deposits in large amounts in the wall, in nerve trunks, in stroma cells and free in the stroma.

The intestines were dull gray, and the mesentery contained numerous small grayish-black lymph nodes. In the ileum were dark pigment granules in the mucosal phagocytes. The mesenteric nodes contained masses of black pigment.

The kidneys showed marked pyelonephritis. Silver granules were found in the glomerular endothelium. Much pigment of a similar type was present in the cortical tubules along the basement membrane but not definitely in the epithelium itself. The cortical and medullary stroma contained much silver, free and in phagocytes. The pelves, ureters and bladder showed chronic inflammation.

AN UNUSUAL MALIGNANT TUMOR IN THE PELVIS OF A 14 YEAR OLD BOY. CLAUDE R. SMITH.

The patient, a white boy, 14 years of age, was first seen by a physician because of retention of urine. His past history, as given by the family, was that he had been below normal mentally all his life, had suffered from epileptic attacks since infancy, and at irregular intervals during the past year had had periods of acute retention of urine.

The patient was well nourished. The only findings of note were a small tumor mass at the right side of the neck and another in the left inguinal region. A rectal examination was not done. A few days later the tumor of the neck was removed for pathologic examination. A diagnosis of metastatic carcinoma of unknown origin was made.

Six weeks later the boy was admitted to the hospital where a large tumor mass was found in the pelvis. The left inguinal and the cervical lymph nodes were enlarged, and tumor masses the size of a hen's egg were found in the left biceps and in the soft tissues of the left forearm. Roentgen examination of the entire skeleton showed no evidence of tumor invasion of the bone, but there were multiple metastases in the lungs. The patient's condition gradually grew worse as urinary obstruction became more marked. Symptoms of renal damage ensued and the nonprotein nitrogen of the blood rose to 110 mg. per hundred cubic centimeters. There was marked cough with blood-tinged expectoration. The patient became comatose and died two months after he was first seen.

At autopsy the most significant finding was a large tumor mass which almost entirely filled the pelvis. The tumor was situated posterior to the bladder and arose apparently either from the prostate gland or from a seminal vesicle. The

adjacent lymph nodes were infiltrated with tumor, and metastases were found in the lungs, in the myocardium and in the muscles of the left arm. The skeleton was not involved.

Sections from the primary tumor of the pelvis showed a highly anaplastic carcinomatous growth forming in some areas atypical spaces suggestive of seminal vesicle mucosa but not without resemblance to the glands of the prostate. Pathologists differed as to the true origin of the tumor, some thinking that the neoplasm was primary in the prostate gland, and others believing that it arose from a seminal vesicle. Evidence at present is in favor of the second possibility. Such tumors are exceedingly rare.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, May 8, 1933

OSCAR T. SCHULTZ, *President pro tempore, in the Chair*

THE CELLULAR INCLUSIONS OF THE SUBMAXILLARY GLAND VIRUS OF GUINEA-PIGS. FLOYD S. MARKHAM AND N. PAUL HUDSON.

The intracellular bodies found by Jackson in the enlarged epithelial cells of the ducts of the submaxillary gland of guinea-pigs were shown by Cole and Kuttner some years later to be associated with the presence of a filtrable virus. In sections of tissues which have been fixed in a diluted solution of formaldehyde or Zenker's solution and stained with hematoxylin-eosin or eosin-methylene blue (methyl thionine chloride, U. S. P.) the intranuclear inclusions generally appear as homogeneous or finely granular acidophilic masses. Unstained sections of fixed tissues mounted in glycerin disclose an intranuclear mass which appears to be composed of small round refractile corpuscles of approximately uniform size. Similar sections stained with hematoxylin and decolorized with picric acid also indicate the corpuscular composition of the inclusion.

Fresh unfixed glands taken directly from infected animals and examined in wet mounts have failed to reveal inclusions of the sort seen in fixed and stained preparations. Instead the hypertrophied nuclei of the epithelial cells appear to contain only a few clumps of extremely fine granular material and a few minute refractile granules in active brownian movement. Vesicular structures resembling the enlarged nuclei free from the cell have rarely been seen in such preparations. These vesicles are studded with small corpuscles like those seen in the inclusions of the hematoxylin-picric acid sections. Within the vesicular membrane on which the corpuscles lie are small clumps and refractile granules like those observed in the nuclei of the swollen epithelial cells.

Because of the variation in morphology under these conditions, one should be exceedingly cautious in interpreting the genesis of the inclusion body and its relation to the virus on the basis of fixed and stained materials.

CHRONIC EMBOLIZATION OF THE LUNG. VICTOR LEVINE.

Chronic embolization of the lung, in which multiple emboli are carried to the lungs for a long time, eventually causes marked obstruction of the pulmonary circulation. A 46 year old colored woman had cough and expectoration for ten weeks, pain in the legs for about nine weeks and dyspnea on exertion for three or four weeks. She had marked swelling of the lower extremities, owing to pressure on the veins by a large fibromyomatous uterus. Fifteen hours before death she had a sudden left hemiplegia, followed by marked dyspnea until death.

At autopsy the uterus was firmly wedged in the pelvis, and there were thrombi in the left ovarian, obturator, both iliac, femoral and uterine veins. The right side of the heart was hypertrophied, and the pulmonary artery was occluded by

an embolus which, because of its size, was considered to have come from the inferior vena cava. The large and medium-sized branches of the pulmonary arteries on both sides were occluded by blood clots, which varied from recent, slightly adherent to old, firmly adherent, organized and canalized. These clots were interpreted as multiple emboli from the thrombosed veins, coming to the lungs in showers at different times.

Not all cases of chronic embolization are as clear as this. There may be multiple thrombosis in the pulmonary arteries without any detectable source of possible emboli. Nevertheless, Deschin, Goedel and Ljungdahl consider that in most of these cases there is chronic embolization. Goedel classifies such cases as due to sclerosis of the vessels, arteritis (including syphilis) or chronic embolization. A number of recent cases called examples of thrombosis of the pulmonary arteries appear, on analysis, to be cases of chronic embolization.

In the case now reported the patient lived fifteen hours after the fatal embolism. This long survival is undoubtedly due to well developed collaterals between the pulmonary and bronchial arteries from the gradual occlusion of the pulmonary arteries by multiple emboli.

Thus, chronic embolization must be added to chronic emphysema, pneumoconiosis, pulmonary arteriosclerosis, deformities of the spine and congenital or acquired narrowing of the pulmonary veins as a cause of right ventricular hypertrophy.

Cases of chronic embolization are rare. In 1930, Deschin collected sixteen cases and added eight of his own. No previously reported case under this title could be discovered in the English literature.

READJUSTMENT OF THE PULMONARY CIRCULATION IN COMPRESSION THERAPY: STUDIES BY THE INJECTION METHOD. W. R. WILLIAMS.

Since the revival of interest in the surgical treatment of pulmonary tuberculosis, there have been numerous contributions concerning the circulatory changes resulting from pneumothorax, phrenicurectomy and thoracoplasty. A group of investigators headed by Cloetta maintains that there exists an equal circulation in the collapsed lung, while another group favors the opinion of Bruns that the circulation in the collapsed lung is lessened. An attempt to explain this diversity of opinion would be unsuccessful unless an analysis was made of all the factors concerned, both cardiac and extracardiac. Such an attempt is beyond the scope of this paper, the purpose of which is to deal initially with the mechanical factors.

The materials used for study were the hearts and lungs of thirty-five rabbits, the lungs of three dogs and the lungs of three men. The technic varied slightly according to the information desired. An effort was made to demonstrate the circulation of the lungs in normal expansion, overdilatation and various degrees of collapse.

The heart and lungs were removed immediately after the death of the animal. The blood was washed out of the heart and the blood vessels with warm water. Success in the experiment depends largely on the absence of blood clots. A cannula was then inserted into the trachea and tied, and a warm solution of gelatin was injected into the lungs until the desired dilatation was obtained. The specimen was then placed in cold water and hardened. By this method any degree of dilatation was maintained. The blood vessels were then given injections of celloidin under continuous pressure for four days, and allowed to harden in water. Then the tissues were corroded with hydrochloric acid and finally washed with running cold water, and the specimen was preserved for study. For the collapse experiment, after washing, the lungs were filled with gelatin to their average normal dilatation. Then the specimen was placed in warm water. Owing to the elasticity of the lung tissue the gelatin was expressed from the lungs. When the desired degree of collapse had occurred, the specimen was placed in cold water and hardened. When collapse of one lung was desired, a ligature was tied below the bifurcation of the trachea, and the other lung was allowed to collapse. The specimens prepared were a cast of the cavities of the heart, the great vessels,

the blood vessels of the lungs and their branches to include the precapillary area. The bronchial artery was not injected. An attempt was made to imitate the appearance of the vessels in various degrees of distention and collapse.

When the thorax was opened the lungs collapsed. Most of the blood had been compressed out of the smaller blood vessels, and had accumulated in the larger blood vessels and the cavities of the heart. The lungs were about one-third their average normal size. An attempt was made to distend the arterial circulation with water to ascertain the difference in the size of the lungs when the arteries were distended. This proved unsuccessful, however, because the blood vessels ruptured, and the air spaces were distended. That this rupture occurred in the smaller arteries was evident because it did not interfere with subsequent filling with celloidin when the walls of the blood vessels were supported by the gelatin. If this part of the experiment had been successful, some information could have been obtained regarding the resistance offered by the collapsed lung.

Uniform distention of the lungs with gelatin was accomplished easily. The resistance offered to subsequent filling of the blood vessels with celloidin, as measured by the amount of pressure required for successful filling, varied with the solidity of the gelatin. A 3 per cent solution was satisfactory. The specimens most successfully filled were those distended to their normal size. The blood vessels were filled to include, but not exceed, the precapillary area. With overdistention the blood vessels became elongated and narrowed. The greater the distention the less successful was the injection. The smaller arteries were obliterated.

The size of the lungs varied with the degree of collapse; this occurred largely at the expense of the alveoli and bronchioles. In the lesser degrees of collapse the smaller arteries were brought closer together. However, they were filled with celloidin. As compression increased and the lungs continued to decrease in size, increased pressure of the injection fluid compensated for this resistance, but only partially. When the compression had advanced to a stage where there was angulation of the smaller blood vessels, they failed to fill, even with increased pressure. Consequently there was dilatation of the larger branches, and they became tortuous. The dilatation due to increased pressure also affected the contralateral lung. This observation is of interest because of the possible influence on cardiac output.

Another interesting observation was made when the pulmonary veins became filled simultaneously with the arteries. This occurred because of defective closure of the foramen ovale, and was noted in three of thirty-five rabbits. The same was observed in nine of thirty-two human hearts obtained for the purpose of studying the coronary arteries. In none of these patients was the condition recognized during life; none died from cardiac disease. The clinical significance is that while intra-auricular pressure is equal on both sides, there are no functional disturbances, while if for any reason (such as mitral stenosis) there is increased unilateral pressure, blood is interchanged between the auricles.

The pericardium was left intact in all specimens. The hearts were distended in some instances to fill the pericardial sac. In one instance the pericardium was accidentally incised. When the heart was filled with the injected fluid it dilated, and finally, at a pressure of 140 mm. of mercury, the right auricle ruptured. An attempt was made to rupture the heart while the pericardium was intact. Pressure up to 300 mm. of mercury failed to rupture either the heart or the blood vessels.

Summary.—Resistance to the pulmonary circulation is increased in proportion to the degree of overdistention or collapse. The increased resistance can be compensated to some extent by increased pressure. With overdistention of the lungs, the blood vessels become elongated, narrowed and obliterated. Compression of the lungs results in tortuosity, angulation and obliteration of the vessels. The blood vessels of the opposite lung are distended. The circulation in the lung varies with, and is dependent on, the degree of overdistention or compression and the functional integrity of the right ventricular myocardium to compensate for the increased resistance.

THECA CELL TUMORS OF THE OVARY. PERRY J. MELNICK.

Two cases of a newly recognized entity, theca cell tumors of the ovary, are reported. Both occurred in women long past their menopause, in whom bleeding began again. In one case the bleeding was periodic, like the normal menstrual cycle. The endometrium in both cases was distinctly hyperplastic, and the uterus large. The tumors were composed of cells which had the histologic characteristics of theca interna cells. Apparently these tumors secreted theelin. This conclusion is supported by much experimental and deductive evidence cited in the literature that the theca cells secrete the estrogenic hormone.

FRIEDLÄNDER'S BACILLUS MENINGITIS SECONDARY TO BILATERAL ACUTE OTITIS MEDIA. G. HOWARD GOWEN.

A woman, aged 63, had influenza in December, 1931, and in the third week of January, 1932, had symptoms which developed into bilateral ruptured otitis media. In May, 1932, an acute right mastoiditis was drained. An abscess appeared in the right posterior triangle of the neck and was drained, but the sinus failed to close. Cultures of the exudate demonstrated *Staphylococcus aureus* and Friedländer's bacillus. Cerebral symptoms began on August 5, and death occurred on August 12. Postmortem examination demonstrated an acute exudative leptomeningitis, and Friedländer's bacillus was identified culturally.

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, May 11, 1933

MORTON McCUTCHEON, *Vice President, in the Chair*

COMPARATIVE STUDIES ON THE DEFICIENCY DISEASES OF BONE IN MAN AND IN MONKEYS. E. P. CORSON-WHITE, R. S. BROMER and IRVIN STEIN.

Experiments have indicated clearly the importance of calcium and phosphorus in bone formation and also the antagonism between vitamin D and phosphorus on the one hand and parathyroid extract-Collip, calcium, magnesium, strontium and even lead on the other. To a certain extent such experimental work has been hindered by the fact that most of it was done on rats. There is a histologic difference in the rat parathyroid as compared with the human, the former being characterized by the absence of oxyphilic cells. Physiologically, it is difficult if not impossible to produce rickets in the rat if the diet contains a sufficient amount of phosphorus, even though vitamin D is absent. In man it is definitely known that an absence of vitamin D will permit the development of rickets even though phosphorus is present in sufficient amounts, or an excess of phosphorus may easily produce a phosphorus rickets characterized by tetany.

The deficiency diseases of bone in monkeys present much the same roentgen appearance as do those in man. In rickets, the changes as observed in an orangutan aged 13 months were widening of the diaphyseal ends, fraying out of the zone of temporary calcification, haziness of outline of the epiphyseal centers and generalized decalcification of the diaphyses as shown by a streaked appearance of the cortex. In osteomalacia extreme thinning of the cortex, generalized decalcification and multiple fractures of the shaft were usually found. In osteitis fibrosa cystica widening of the ends of the shafts due to bone cysts and giant cell tumors, together with marked thinning of the cortex, generalized decalcification and occasionally increased trabecular shadows, were noted. In Paget's disease, the appearance is that of osteomalacia, except that increased density of the cortex occurred in scattered areas with increased porosity of bone in others. The tables

of the skull were thickened as in man, with scattered areas of decreased density and decalcification. No case of osteoporosis circumscripta or localized Paget's disease was found in the live monkeys and museum specimens examined.

Metabolic studies of these conditions in both man and monkeys yielded similar results. Rickets could not be compared, as it has been impossible to obtain monkeys sufficiently young for such work. Most authorities consider osteomalacia as an adult rickets. The researches of Miles and Chih Tung on osteomalacic women and our studies of seven osteomalacic monkeys showed a constant definite loss of calcium and a retention of phosphorus, magnesium and sulphur together with a lowered serum calcium and phosphorus content. In osteitis fibrosa cystica there was a marked loss of calcium and phosphorus in the urine and feces and a high serum calcium content associated with a low value for serum phosphorus. One monkey with this condition was studied and gave the same results. In Paget's disease the metabolic findings in five human subjects and three monkeys were a retention of calcium, phosphorus and magnesium and a constant loss of sulphur. The values for serum calcium and phosphorus in both groups were normal or very close to normal.

These results indicate that for the study of these bone diseases the monkey is more valuable than the rat. The deficiency diseases of bone are considered by us to be similar in man and monkeys.

Work is now in progress on the possible relationship of these diseases and on the evaluation of the parathyroid factor.

TORULOSIS IN MAN, THE CHEETAH AND EXPERIMENTAL ANIMALS. FRED D. WEIDMAN and HERBERT L. RATCLIFFE.

Torulosis of man, i. e., infection by *Torula histolytica*, is essentially a disease of the central nervous system. Clinically, it most often simulates tuberculous meningitis. Involvement of the brain and cord takes the form of a chronic meningo-encephalitis. Histologically, the membranes are more or less diffusely thickened by fibrosis and an accumulation of large mononuclear cells. This tissue is loosely arranged and contains large numbers of free and phagocytosed yeast cells. Within the brain the cortical tissues and basal ganglions are usually involved by varying numbers of small, single or multilocular cysts disposed around vessels. These contain a jelly-like substance which, in section, is made up of masses of yeast cells proliferating and expanding without any important reaction on the part of the surrounding tissue.

A case of torulosis was discovered in a cheetah, or hunting leopard, *Cynaelurus jubatus*, dying in the Philadelphia Zoological Garden. The animal showed a much more generalized infection than is usual for man, indeed probably the most extensive on record. The lesions consisted of a chronic cystic meningo-encephalitis, massive diffuse involvement of the spleen, kidneys and retroperitoneal lymph nodes and miliary foci in the liver, lungs, mesenteric lymph nodes, suprarenals and pancreas. The reaction in the central nervous system was similar to that in man. The spleen was hugely enlarged and may be described as simply an encapsulated mass of yeast cells, necrotic debris and mononuclear leukocytes with but scattered remnants of splenic tissue. Hemorrhages were numerous. The kidneys contained large numbers of small granulomas, and much of the intervening tissue was densely infiltrated by lymphocytes and plasma cells. The granulomas were made up of proliferating fibrous tissue which was infiltrated by monocytes. Free and phagocytosed yeast cells were numerous in these areas. Colonies of yeast cells were also found in glomeruli and tubules, unaccompanied by inflammatory response. All of the lesions within the liver, lungs, pancreas, mesenteric lymph nodes and suprarenals were of microscopic size and made up of monocytes and giant cells which replaced the normal tissues and had phagocytosed many of the yeast cells. The parasites were also present in spaces between the inflammatory cells and occasionally within blood vessels that remained in the lesion.

Cultures were not attempted from the cheetah, but twenty strains of *T. histolytica* were injected intrameningeally into five cats and twenty-eight white rats. Lesions did not develop in the cats. In the rats there were nine instances of generalization (lungs, spleen, liver, kidney and pancreas) besides involvement of the brain and spinal cord. In no case were cysts recognizable grossly, probably because the lesions did not have time to develop fully. Microscopically, however, both the torular and tissue reactive changes were similar to those in man. In a monkey, inoculated subcutaneously, frank and permanent lesions developed locally, but without generalization.

The outstanding points of the presentation were the observations on the cheetah: (1) the occurrence in a wild animal, though in captivity (only one other case has been reported in an animal, a horse); (2) the widespread generalization with massive involvement of the spleen and kidneys; (3) the remarkably thick, apparently mucinoid envelop around the parasites; (4) the extremely wide range of type of tissue reaction, and yet (5) no participation by leukocytes; (6) a negligible reaction in the brain tissue even in the presence of large cysts crowded with parasites, and (7) the absence of polymorphonuclears.

AGRANULOCYTOSIS AND ACUTE LEUKEMIA. MAX M. STRUMIA.

1. Evidence gathered from the clinical course, the hematologic picture and the anatomic lesions occurring in agranulocytosis and acute leukemia points to many similarities between the two conditions. These are made more convincing by at least six cases of transition of one form into the other, three of them being presented in this paper, one with recovery. The essential lesion which dominates both pictures seems to be a disturbance of the bone marrow, when the mature and undifferentiated parent cells become incapable of maturation. This lesion is very likely based on a constitutional imperfection of the hematopoietic system, congenital or acquired. The rôle played by intercurrent infections, toxemias or susceptibility to various substances is probably a deciding, but not necessarily a specific, factor. An essential difference between the two forms seems to be in the mechanism of release of the immature and undifferentiated cells in the circulating blood, a release which occurs in acute leukemia but not in agranulocytosis.

2. On the basis of theoretical considerations regarding the normal maturation of granulocytic cells, suspensions of normal leukocytes from the human blood have been employed in the treatment of neutropenia. Definite evidence has been gathered that the injection of a leukocytic suspension intramuscularly greatly stimulates the maturation of granulocytic cells. So far, ten patients with agranulocytosis have been treated, and all recovered. In nine of them the favorable effect of the leukocytic suspension appears to be unquestionable. Concerning the tenth patient, the conclusion is doubtful, because of the numerous other therapeutic measures employed and because of the insufficient hematologic data available at the present time.

The stimulating effect of intramuscular injections of a leukocytic suspension has also been demonstrated in neutropenia of other types (acute leukemia, severe infection and malignant tumor).

A SIMPLIFIED ACETONE-GIEMSA STAINING METHOD FOR BLOOD SMEARS. JOHN EIMAN.

This method is recommended for use in routine blood counts. It gives a picture practically similar to that obtained by the acetone-Giemsa method but is much more simple in application and considerably less expensive. The steps of the method are: (1) Fix the blood smears in methyl alcohol for from three to five minutes; (2) immerse the slides for ten minutes in a Coplin jar containing the acetone-Giemsa stain diluted with distilled water 1:10 (this dilution is good for about twelve hours); (3) dry the smear without washing.

The acetone-Giemsa stain is prepared by mixing equal parts of Grübler-Giemsa's solution with chemically pure acetone. The reaction with the distilled water is of

utmost importance. If the water is too acid, the film of blood is going to be rather bright pink, and granules of neutrophils will be eosinophilic. If the water is too alkaline, the smear will have a bluish-green appearance, and neutrophilic granules will be dark bluish. When the reaction of the water is right, the smear will have a slightly bluish-green tint in the thicker portions, neutrophilic granules will be truly neutrophilic, and the platelets will have a pale purplish appearance. To correct the reaction usually the addition of either a drop of a 1 per cent solution of sodium carbonate or a drop of 0.5 per cent glacial acetic acid to 1,000 cc. of distilled water is sufficient. Attempts to buffer the water and to adjust it to the desirable p_H have not been successful.

Book Reviews

The Biology of the Protozoa. By Gary N. Calkins, Ph.D., Sc.D., Professor of Protozoology, Columbia University, New York. Second edition, thoroughly revised. Cloth. Price, \$7.50, net. Pp. 607, with 223 engravings and 2 colored plates. Philadelphia: Lea & Febiger, 1933.

This work does not attempt a comprehensive account of protozoology, but is a study of biology as represented by the protozoa. The author attempts to present "the concept of a changing organization brought about by continued metabolism" and to use it for the interpretation of life cycles, reproduction, maturation and senescence. A brief section on parasitism and disease is added in this edition in recognition of the fact that they should be included in any consideration of general biology.

The volume contains fourteen chapters. Chapter I forms an introduction and deals with the size, form and appearance of protozoa. The fundamental organization is given in chapter II, and the derived organization in chapters III and IV. A general account of physiology forms chapter V. Chapters VI, VII, VIII and IX comprise a closely integrated series dealing with methods of reproduction, vitality, phenomena accompanying fertilization, effects of reorganization and the origin of variations in the protozoa. Chapter X deals with general ecology, commensalism and parasitism. The last four chapters (XI, XII, XIII and XIV) comprise special morphologic and taxonomic considerations of Mastigophora, Sarcodina, Infusoria and Sporozoa.

Throughout the author is to be congratulated on his physiologic point of view and his stress of experimental methods. Although he has accumulated a mass of data, most of it has been carefully digested and arranged in a logical treatment in which his own views are repeatedly manifest. This is nowhere better shown than in his treatment of the questions of vitality, reorganization and rejuvenescence, a field in which Professor Calkins' views are of particular interest to protozoologists because of his many contributions to it. In brief, he believes, as suggested by Child, that "senescence consists in a decrease in metabolic rate determined by the change in, and the progressive accumulation of, the relatively stable components of the protoplasmic substratum during growth, development and differentiation." In some protozoa, such as the animal flagellates in which fertilization processes are unknown, it seems probable that the reorganization after each cell division is accompanied by sufficient rejuvenescence to overcome these progressive senescent changes and to allow indefinite asexual reproduction. In other cases (notably the ciliates) in which cell division does not leave the cell in its original labile condition, a progressive aging occurs as asexual reproduction proceeds so that such a line gradually becomes senescent and eventually dies out unless the reorganization and the concomitant rejuvenescence of endomixis or conjugation intervene. In these forms there is essentially the natural death after a typical life cycle as originally postulated by Maupas. Although he disagrees with Woodruff's contention that the loss of vitality is not due to intrinsic aging but to insufficient culture methods, he does stress the changes in the life cycle due to environmental stimuli. As he aptly states in the preface, if the self-regulating mechanisms of reorganization are recognized the protozoa are potentially immortal in the sense of Weismann, but not each a potential germ cell as postulated by Weismann.

Pathologists and parasitologists will be particularly interested in chapter X in which the protozoa are divided into six ecologic groups: those that are water-dwelling, semiterrestrial, soil dwelling, sapropelic, coprozoic and parasitic. The major part of the chapter deals with the parasites. Although the specialist might question some of the specific statements, the descriptions of the groups are in general excellent, but necessarily limited. Nor will the

specialist find a general technical account of the parasites, but the entire book is recommended to all such workers as a biologic survey which places the parasitic protozoa in their proper relationship to the free-living forms and treats them as a special ecologic group. This is of particular importance because there has always been a tendency for the parasitologist to consider parasites as things apart about which to build special philosophical systems, forgetting that the main generalizations should apply primarily to free-living forms and secondarily to the specialized parasites.

The entire book is beautifully illustrated to a large extent with drawings by the author. There are a compact bibliography covering eighteen pages and a complete index.

La spécificité biologique. Anaphylaxie, immunité, hérédité. By M. Martiny, H. Prétet and A. Berné. Price, 35 francs. Pp. 209. Paris: Masson & Cie, 1932.

One of the chapters of the book is preceded by a phrase of Pasteur: "Imagination should lend wings to the thought." That phrase and a statement in the introduction that it is the wish of the authors that the ideas expressed in the book be considered merely as a working hypothesis and as a starting point for further experimentation must be kept in mind when one evaluates the contents of the book. The burden of proof is passed on to future experimental investigators. Having accepted such premise, the critical reader can follow the authors through a discussion of some basic principles of immunology.

A. Berné, a physical chemist, is responsible for the chapters dealing with physics and chemistry. The central idea of the work is the conception that the antibody is a modified antigen. The authors profess the unitary conception of the antibodies. A. Berné has developed a hypothesis of his own on the structure of the atom. The other two authors have applied it, as well as some of his other ideas, toward the elaboration and substantiation of the hypothesis on the origin of the antibody. The essential change occurring in the antigen after its introduction into the animal body is the depolymerization of its molecule, during which process the high dilution in the body fluids is a prime, though not the only, factor. The diluted antigen attaches itself to the globulin of the serum. The diluted, depolymerized, antigenic molecule has a certain characteristic vibratory frequency which is different from the frequency of the subsequently freshly introduced antigen. The two substances, though chemically identical, are like two identical, but differently tuned musical instruments. The frequencies, while different, are harmonious, and as a result of resonance the molecules of the antigen combine by polymerization and thus increase in size. After a certain maximum size is reached, flocculation occurs. In that process the antibody plays the rôle of an autocatalyzer. Great emphasis is laid on the very high dilutions of the antigen, and, therefore, in the theoretical and in the experimental chapters infinitesimal quantities are employed. In this and in other respects the homeopathic inclinations of the authors are evident.

The first chapter of the book, which covers the history of the concept of biologic specificity, is followed by seven chapters dealing with newer developments in certain fields of physics, with the physical chemistry of antigens, with specific antibodies, with the antigen-antibody reaction, with anaphylaxis and hypersensitiveness, with immunity in infectious diseases, with heredity and with biologic and therapeutic individuality. Nineteen pages of the appendix give highly theoretical, physical and chemical considerations, heavily loaded with higher mathematics, and the final fifteen pages are a record of the experimental work which was done in an attempt to solve the following problem: If the antibody is a diluted and depolymerized antigen, then it ought to be possible, for instance, to neutralize diphtheria toxin with proper dilutions of the same toxin in vitro or in vivo, or in both ways. No support whatsoever was supplied by any of the

numerous experiments. More successful was the attempt to produce anaphylaxis in guinea-pigs by sensitizing them with infinitesimal quantities of egg albumin. They received by mouth quantities varying from 5 cc. of a 1:1,000,000,000 dilution to 5 cc. of a 1:1,000,000,000 dilution. When the guinea-pigs were given other injections intracardially of 0.5 cc. of a 1:100 dilution of egg albumin after intervals varying from one to forty-eight hours, they showed unmistakable signs of moderate to marked anaphylactic reactions. Similar results were obtained in animals prepared with subcutaneous injections. The sensitization was of a transient nature and was not uniform. Many animals failed to react.

The book ends with an expression of hope that experimental evidence will be forthcoming. The book is interesting, stimulating and well written.

Histopathology of the Peripheral and Central Nervous Systems. By George B. Hassin, M.D., Professor of Neurology, University of Illinois College of Medicine; Attending Neurologist, Cook County Hospital, Chicago. Price, \$5.50. Pp. 491, with 229 figures. Baltimore: William Wood & Company, 1933.

"Though neuropathology is essential to an understanding of clinical phenomena, it is given rather inadequate space in ordinary clinical manuals on neuro-psychiatry. To fill the gap, I have prepared the present volume. It embodies largely the results of twenty years' work in the field of histopathology of the nervous system. Diseases of the peripheral nerves, spinal cord and brain are described individually, from a histopathologic angle only, as they are in textbooks on clinical neurology. The frequent references to the clinical aspects of the subject have purposely been made very brief." This statement in the author's preface describes accurately the scope, the general character and the purpose of this latest American book dealing with the structural changes in the nervous system. The title of the book is accurately descriptive. Knowledge of the microscopic structure of normal nerve tissues, even as revealed by the newer methods of study, is taken for granted, and the author plunges at once into the description of morbid nerve structures. The book is divided into four parts: diseases of the peripheral nerves and muscles, diseases of the spinal cord, diseases of the brain, and staining methods. The 229 figures, mostly original, nearly all photographic, illustrate well the morphologic descriptions of the text. One misses a really good illustration of gitter cells, of which there is much talk in the book. At the end of each chapter is a list of helpful references to the recent literature of the subject discussed. A few questions and comments, largely of minor nature, suggest themselves. Is not epidemic poliomyelitis a much more commonly used name nowadays than either acute anterior poliomyelitis or Heine-Medin's disease? Why include certain forms of tuberculosis and other granulomatous diseases under tumors in the case of the spinal cord and not in the case of the brain? Why include them under tumors in any case? To the student such inclusion cannot but be confusing. And why long, separate descriptions under inflammation of so-called "carcinomatous meningitis and pachymeningitis?" By the way, the description and naming of gliomas are fully up-to-date. Trichinosis encephalitis and trichiniasis encephalitis and like combinations should be avoided. The cerebrospinal fluid does not receive any consideration. The statement on page 442 that botulism is "poisoning with decayed meat" needs correction. In the index, which should have been made more elaborate, rabies is listed only under encephalitis. The presentation is orderly, systematic and comprehensive. The descriptions of the microscopic appearances are accurate and thorough, but the language is not always simple and clear. At times the description becomes almost more detailed and minute than necessary. The learned and conscientious author has spared no pains to explain fully the complicated microscopic structural basis of diseases of the nervous system as now understood, and there is no question concerning his complete mastery of the subject. Hassin's book, at the moment, stands as a leader in its field, and it will be of great help to all who are interested in the microscopic morphology of nervous diseases.

Die Histopathologie der Uterusmucosa. Ein Leitfaden für Gynäkologen and Pathologen bei der histologischen Diagnostik. By Dr. H. T. Deelman, Ord. Prof. der allgemeinen Pathologie und pathologischen Anatomie der Reichsuniversität Groningen. Paper. Price, 22 marks. Pp. 247, with 248 illustrations. Leipzig: Georg Thieme, 1933.

This book is written as a guide to the microscopic diagnosis of the endometrium. It is the product of the thorough study for ten years of material submitted to the author by his gynecological colleagues. There are eight chapters. The first deals with the endometrium in pregnancy, uterine and extra-uterine. The various normal and abnormal changes that may occur in the endometrium in connection with pregnancy are described and illustrated. The second chapter is devoted to hydatid mole and choriocarcinoma. About thirty-three figures illustrate the appearances described in this chapter. Chapter three presents the microscopic appearances in endometritis, including the tuberculous form. In the fourth chapter the author describes various atypical conditions in the uterine mucous membrane due to vital as well as to traumatic influences. Then there is a chapter on uterine polyps and other nonmalignant tumors of the endometrium. The sixth chapter is occupied with carcinoma of the uterus and its microscopic diagnosis. Nearly fifty figures are used to elucidate the descriptions. Epidermoid and other carcinomas of the cervix are not considered. The seventh chapter is concerned with endometrial hyperplasia and the effects of the menstrual cycle on the endometrium. The relations of endometrial hyperplasia to hormonal influences are considered. The final chapter describes the uterine mucosa in the climacteric. The presentation is based almost entirely on material obtained from individual cases, which are described briefly. The excellent illustrations, all original photomicrographs, reproduce appearances observed in the microscopic study of this material. Consequently there is the closest possible relation between the text and the illustrations. All who are actively concerned in the microscopic examination of the endometrium for diagnostic purposes will welcome this book warmly. It is a modern and highly efficient guide in its field.

Lymphatics, Lymph and Tissue Fluid. By Cecil K. Drinker, B.S., M.D., Professor of Physiology, Harvard School of Public Health, and Madeleine E. Field, A.B., Ph.D., Instructor of Physiology, Harvard School of Public Health. Price, \$3. Pp. 254. Baltimore: Williams & Wilkins Company, 1933.

This is a clear, concise and therefore readable and authentic volume on the known and the probable in the matter of lymph, lymphatics and the production of lymph in health and in disease. The volume is the outcome of the senior author's interest and work on certain phases of the problem of lymph for a number of years. The eight chapters deal with the histogenesis and structure of the lymphatic system; the entrance of foreign matter and colloidal solutions into the lymphatics; the permeability of the blood capillaries and its bearing on the production of lymph; the mechanics of the flow of lymph; the chemical composition of lymph and tissue fluids; assays on lymph in circulatory edema, in hypertension, under conditions of lowered plasma proteins, asphyxia, anaphylactic shock and inflammation, and as affected by heat and light. Investigators in the fields of normal and pathologic physiology, surgery, internal medicine and physical therapy will find the monograph a storehouse of information, keen analysis and clear discussions.

Books Received

STUDIES FROM THE INSTITUTE FOR MEDICAL RESEARCH, FEDERATED MALAY STATES, No. 21, KUALA LUMPUR: MELIOIDOSIS. A. T. Stanton, C.M.G., M.D., F.R.C.P., Chief Medical Adviser to the Secretary of State for the Colonies; formerly Director of Government Laboratories, F.M.S.; and William Fletcher, M.D., M.R.C.P., Member, Colonial Advisory Medical Committee; formerly Director, Institute for Medical Research, F.M.S. Pp. 59, with 37 figures. London: John Bale Sons & Danielsson, Ltd., 1932.

HISTOPATHOLOGY OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEMS. George B. Hassin, M.D., Professor of Neurology, University of Illinois College of Medicine; Attending Neurologist, Cook County Hospital, Chicago. Price, \$5.50. Pp. 491, with 229 figures. Baltimore: William Wood & Company, 1933.

THE BIOLOGY OF THE PROTOZOA. Gary N. Calkins, Ph.D., Sc.D., Professor of Protozoology, Columbia University, New York. Second edition, thoroughly revised. Price, cloth, \$7.50, net. Pp. 607, with 223 engravings and 2 colored plates. Philadelphia: Lea & Febiger, 1933.

MEDICAL RESEARCH COUNCIL REPORTS OF THE COMMITTEE UPON THE PHYSIOLOGY OF VISION: XI. INDIVIDUAL DIFFERENCES IN NORMAL COLOUR VISION. A SURVEY OF RECENT EXPERIMENTAL WORK (1910-1931). W. O'D. Pierce. Price, 2s., net. Pp. 93. London: His Majesty's Stationery Office, 1933.

TUBERCULOUS BACILLAEMIA. G. S. Wilson, with Appendices by Herta Schwabacher, C. C. Okell and E. A. Wood. Medical Research Council, Special Report Series, No. 182. Price, 2s. 6d., net. Pp. 146. London: His Majesty's Stationery Office, 1933.

REPORTS ON BIOLOGICAL STANDARDS: III. METHODS OF BIOLOGICAL ASSAY DEPENDING ON A QUANTAL RESPONSE. J. H. Gaddum. Medical Research Council, Special Report Series, No. 183. Price, 1s. net. Pp. 46. London: His Majesty's Stationery Office, 1933.

KLASSIFIKATION DER SCHIZOMYCETEN (BAKTERIEN); VERSUCH EINER WISSENSCHAFTLICHEN KLASSIFIKATION DER BAKTERIEN AUF BOTANISCHER GRUNDLAGE. Prof. Dr. Ernst Pribram, D. Z. Professor für Bakteriologie und Präventiv-Medizin an der Loyola University, School of Medicine, Chicago. Pp. 119. Vienna: Franz Deuticke, 1933.

DIE NORMALE UND PATHOLOGISCHE PHYSIOLOGIE DER MILZ. Dozent Dr. Ernst Lauda, Assistent der ii. medizinischen Universitätsklinik in Wien. Price, 18 marks. Pp. 277, mit 2 Abbildungen im Text. Berlin: Urban & Schwarzenberg, 1933.

BULLETINS FROM THE INSTITUTE FOR MEDICAL RESEARCH, FEDERATED MALAY STATES. No. 2 OF 1933: THE WATER SUPPLIES OF THE FEDERATED MALAY STATES, NOTES ON SOME OF THE WATER SUPPLIES DERIVED FROM JUNGLE STREAMS AND RIVERS. R. W. Blair. Pp. 162. Kuala Lumpur: Kyle, Palmer & Co., Ltd., 1933.

THE SCIENCE OF RADIOLOGY. Various Contributors. Edited by Otto Glasser, Ph.D. Price, \$4.50. Pp. 450, with 106 illustrations. Springfield, Ill.: Charles C. Thomas, 1933.

BONE MARROW IN AGRANULOCYTOSIS (PERNICIOUS LEUKOPENIA)

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INTRODUCTION

In the first cases of agranulocytosis which were described by Werner Schultz,¹ the complete absence of granulated cells from the bone marrow of the ribs and femur was the outstanding anatomic feature. The bone marrow was fatty with small islands of lymphoid cells among which a few myeloblasts could be distinguished. Many of the subsequent investigators were able to confirm this statement, stressing the integrity or hyperplasia of the erythropoietic tissue and megakaryocytes in striking contrast to the complete aplasia of the granulocytes (Isaacs,² Jackson,³ Koch,⁴ Licht and Hartmann,⁵ Oppikofer,⁶ Petri,⁷ Richards,⁸ Schaefer,⁹ Uffenorde¹⁰ and others). Several authors observed severe alterative changes of the myeloblasts and myelocytes. Thus, Oppikofer reported that the bone marrow in his cases contained numerous myeloblasts which were either degenerated or necrotic. Rotter¹¹ described cells with a deeply basophilic and vacuolated cytoplasm and with large pale nuclei containing several nucleoli. He identified the cells which did not give the oxydase reaction with degenerated myeloblasts and myelocytes. Similar cells were found by Koch, and Hueber¹² mentioned myelocytes with vacuoles in the cytoplasm. Rose and Houser¹³ observed cells with indistinct, ragged outlines and with hyaline droplets in the cytoplasm in the hyperplastic bone marrow in a typical case of agranuo-

From the Department of Pathology of the Cook County Hospital and the Uihlein Memorial Laboratory of Grant Hospital.

1. Schultz, Werner: *Deutsche med. Wchnschr.* **48**:1494, 1922.
2. Isaacs, R.: *Am. J. Path.* **12**:142, 1931.
3. Jackson, H.: *Arch. Path.* **4**:324, 1927.
4. Koch, W.: *Verhandl. d. deutsch. path. Gesellsch.* **25**:53, 1930.
5. Licht, H., and Hartmann, E.: *Deutsche med. Wchnschr.* **51**:1518, 1925.
6. Oppikofer, E.: *Beitr. z. path. Anat. u. z. allg. Path.* **85**:165, 1930.
7. Petri, E.: *Deutsche med. Wchnschr.* **50**:1017, 1924.
8. Richards, C. V.: *Arch. Int. Med.* **48**:793, 1931.
9. Schaefer, R.: *Deutsches Arch. f. klin. Med.* **151**:191, 1926.
10. Uffenorde, H.: *Virchows Arch. f. path. Anat.* **287**:555, 1932.
11. Rotter, W.: *Virchows Arch. f. path. Anat.* **258**:17, 1925.
12. Hueber, W.: *Frankfurt. Ztschr. f. Path.* **40**:312, 1930.
13. Rose, E., and Houser, K. M.: *Arch. Int. Med.* **43**:533, 1929.

cytosis. The nuclei of these cells were either pale and ballooned or pyknotic, and some of the cells were completely transformed into a hyaline mass. In one of the cases described by van den Wielen¹⁴ the bone marrow contained many cells the size of myelocytes, with small pyknotic nuclei and without granulation. Uffenorde spoke of large cells with a pale cytoplasm and various forms of nuclear degeneration. Hartwich¹⁵ and Petri had difficulty in classifying the atypical cell forms which they encountered in the bone marrow.

According to Fried and Dameshek,¹⁶ there is often a widespread necrosis of the leukopoietic tissue in the severe forms of agranulocytosis, a statement which was also made by Naegeli¹⁷ in the recent edition of his textbook. In two of his four cases of agranulocytosis, Koch found foci of necrosis in the bone marrow, liver and spleen.

In the bone marrow deprived of its granulated elements small lymphocytes are often present in great number (Koch, Petri, Uffenorde, Zikowsky,¹⁸ Zadek,¹⁹ Rotter, Hueber, Komerell²⁰ and others), and the small lymph follicles which are common in normal bone marrow may be conspicuous (Hallermann²¹). Koch, Baltzer²² and Zikowsky described plasma cells, and Rotter, Hallermann, Koch and W. Schultz and Jacobowitz²³ reported on hyperplasia of the reticulohistiocytic elements which may show erythrophagocytosis and iron pigmentation.

The cases of agranulocytosis in which the bone marrow reveals severe alterative changes or complete exhaustion of the granulopoietic tissue are in contrast to those cases in which the bone marrow is found to be normal or hyperplastic without apparent injury to the granulopoietic tissue. In 1925, David²⁴ described a case of marked neutropenia in which the bone marrow contained many myeloblasts, myelocytes and neutrophilic leukocytes. He suggested a disturbance in the emigration of the mature leukocytes from the bone marrow. His case, however, is not typical since there was a severe anemia associated with the agranulocytosis. Reichenbach's²⁵ patient showed at autopsy a fatty bone marrow with cellular areas which were chiefly composed of promyelocytes. These promyelocytes were well preserved, and only a few

14. van den Wielen, K.: *Frankfurt. Ztschr. f. Path.* **44**:34, 1932.

15. Hartwich, A.: *Ergebn. d. inn. Med. u. Kinderh.* **41**:202, 1931.

16. Fried, B. M., and Dameshek, W.: *Arch. Int. Med.* **49**:94, 1932.

17. Naegeli, O.: *Blutkrankheiten und Blutdiagnostik*, ed. 5, Berlin, Julius Springer, 1931.

18. Zikowsky, J.: *Wien. klin. Wchnschr.* **44**:203, 226 and 259, 1931.

19. Zadek, J.: *Med. Klin.* **21**:688, 1925.

20. Komerell, B.: *Med. Klin.* **25**:1816, 1929.

21. Hallermann, W.: *Folia haemat.* **42**:1, 1930.

22. Baltzer, H.: *Virchows Arch. f. path. Anat.* **262**:681, 1926.

23. Schultz, W., and Jacobowitz: *Med. Klin.* **21**:1642, 1925.

24. David, W.: *Med. Klin.* **21**:1229, 1925.

25. Reichenbach, G.: *Folia haemat.* **45**:376, 1931.

of them contained vacuoles. Reichenbach agreed with the explanation offered by David. He failed to report on the blood changes during life. In one of the cases of Dameshek and Ingall²⁶ in which a sternal biopsy was done during life the bone marrow showed nothing abnormal. Zikowsky, who had at his disposal numerous carefully studied cases of agranulocytosis, observed considerable differences in the cellular picture of the bone marrow. He believes that in the early stages of agranulocytosis there is a blockade of the bone marrow which prevents the mature granulocytes from entering the blood stream. If this blockade persists over a longer period of time, the parental cells of the granulocytes degenerate and break down. Fitz-Hugh and Krumbhaar²⁷ gave a detailed histologic account of the hyperplastic bone marrow in a case of agranulocytosis. Although mature neutrophilic and eosinophilic leukocytes were absent, there was an abnormal number of young myelocytes with pale nuclei and many neutrophilic granules. These young myelocytes formed 20 per cent of the bone marrow cells. Fitz-Hugh and Krumbhaar came to the conclusion that at least occasionally death may occur in an uncomplicated agranulocytic angina with a profound peripheral leukopenia while the leukopoietic centers are well supplied with parental cells. They consider it likely that a maturation factor is at work either arresting the development of the white cells or producing degenerative changes in them before sufficient development has taken place for the migration into the blood stream. In a subsequent paper with Comroe, Fitz-Hugh²⁸ again put the maturation arrest before the primary aplasia of the granulopoietic tissue of the bone marrow. The presence of apparently normal myeloblasts and myelocytes in the bone marrow in some of the cases of agranulocytosis was also stressed by Naegeli¹⁷ and Leuchtenberger.²⁹

The brief discussion of the literature on the condition of the bone marrow in agranulocytosis discloses a great variety of observations which, at the first glance, is difficult to reconcile with the conception that agranulocytosis is a definite disease entity. In compiling the summary of the literature, many cases reported as agranulocytosis had to be eliminated. In some of the reports the description of the bone marrow is so incomplete that no conclusion can be drawn as to its actual appearance. A considerable number of cases do not belong to the group showing typical agranulocytosis but are more related to cases of aplastic anemia (panmyelophthisis) or aleukia hemorrhagica (Frank).

In a series of cases of agranulocytosis I have observed peculiar changes in the myelocytes which, according to my knowledge, have not

26. Dameshek, W., and Ingall, M.: *Am. J. M. Sc.* **181**:502, 1931.

27. Fitz-Hugh, T., and Krumbhaar, E. B.: *Am. J. M. Sc.* **183**:104, 1932.

28. Fitz-Hugh, T., and Comroe, B. J.: *Am. J. M. Sc.* **185**:552, 1933.

29. Leuchtenberger, R.: *Folia haemat.* **39**:63, 1929.

yet been reported. In view of the great interest which has been given in recent years to the problem of agranulocytosis, a description of these changes seems to be warranted. They may also help clear the much disputed question whether or not there is an essential difference between so-called idiopathic and symptomatic agranulocytosis. In the majority of the cases bone marrow was taken from the ribs, the vertebrae and the upper third of the diaphysis of the femur. Since the paper deals with fine morphologic changes, stress will be laid chiefly on the bone marrow of the femur. In my experience, even the most careful decalcification interferes somewhat with the Romanowsky stains. Concerning the technic, I refer to my previous publication on the erythropoiesis in leukemia.³⁰ The optic used consisted of a Zeiss apochromatic oil immersion lens (num. ap. 1.30, f:1.5 mm.) and a compensation eye piece no. 15.

REPORT OF CASES

So-Called Idiopathic Agranulocytosis.—CASE 1.—A white woman, aged 57, with an illness of three weeks' duration, stated that during the past winter she had rheumatic pains and had suffered from an attack of "flu," during which her temperature rose to 103 F. for seven days. She never recovered completely from this attack. In May, 1932, her throat became very sore, and an abscess developed in the right tonsil. Since her condition did not improve under the care of her doctor, she entered the hospital on May 20, 1932. She appeared very toxic, with a slight icteric tint to the skin and sclerae. The temperature varied between 100.2 and 102 F. Both tonsils were transformed into ulcers that were covered by a foul-smelling necrotic tissue. There was a furuncle over the wrist of the left hand. The urine contained many hyaline and granular casts and single pus cells. Albumin was present (4+). The Wassermann and Kahn reactions were negative. The blood cultures remained sterile for ten days. The blood picture showed: hemoglobin (Dare), 70 per cent; erythrocytes, 4,000,000; white cells, 800; lymphocytes, 70 per cent, and monocytes, 30 per cent. In spite of two blood transfusions, the patient died two days after admission to the hospital.

The pathologic anatomic diagnosis was: severe ulcerative pharyngitis; beginning necrosis of the skin of the left side of the neck with marked edema of the subcutaneous tissue; hemorrhagic serous parotitis of the right side; hyperplasia of the peribiliary lymph nodes; infectious softening of the spleen (weight of the spleen, 385 Gm.); moderate fatty changes of the liver; passive congestion of the kidneys with arteriosclerotic pitting; focal interstitial myocarditis (weight of the heart, 350 Gm.); strawberry gallbladder; ancient supracervical hysterectomy, bilateral salpingectomy and oophorectomy, and slight icterus.

On macroscopic examination the bone marrow of the femur appeared soft and reddish brown, with small light yellow areas. Microscopically, many foci of cells were found which formed 27 per cent of the bone marrow, while the rest consisted of fat tissue. In addition to the cellular foci, there were single small lymph follicles. The capillaries and sinusoids were congested with blood. The reticular cells were not swollen.

The cellular foci were composed of the following elements: myeloblasts, 1.24 per cent; neutrophilic myelocytes, 34.4 per cent. These cells were on the average

30. Jaffé, R. H.: *Folia haemat.* 49:51, 1933.

larger than the forms seen in normal bone marrow. Their outlines were often irregular with pseudopodia-like protrusions. The nuclei were oval and showed a distinct membrane and several chromatin granules which were connected by fine threads. The cytoplasm stained a light purple blue with azure II-methylthionine chloride, U.S.P. (methylene blue). The granules were severely changed. Only a few of the cells revealed single intact purple-red granules near the nucleus. In the majority of the cells the granules were swollen, ill defined and transformed into pink specks which seemed to fuse with the cytoplasm (fig. 1). In some of the cells with intact granules mitotic figures were seen. There were 1.80 per cent erythrogonia, 20.39 per cent erythroblasts and 19.85 per cent normoblasts. The segmentation of the nuclei of the normoblasts started before pyknosis had obscured the chromatin structure. The nuclear segments showed, therefore, a coarse chromatin net. There were 0.35 per cent megakaryoblasts and 2.30 per cent megakaryocytes. The majority of the megakaryocytes had lost their granulation, and their nuclei were pyknotic. There were 12.41 per cent lymphocytes and 5.67 per



Fig. 1 (case 1).—Bone marrow showing different forms of degeneration of the neutrophilic myelocytes. Note the transformation of the granules into ill-defined specks. In *A*, vacuoles can be seen about some of the granules. The nuclei are still well preserved. In the center of *A* is a mitosis which is not in the focus. In *B*, plasma cells and lymphocytes appear between the myelocytes. Zenker-formaldehyde fixation; Giemsa stain; magnification, $\times 1,200$.

cent plasma cells. Some of the plasma cells were large and contained two nuclei. There were 1.54 per cent monocytoïd cells.

Among the histologic changes in the other organs, I mention the absence of oxydase positive cells from the spleen, the pulp of which contained many plasma cells and mobilized histiocytes. After a long search, a single myelocyte with scanty granules was found in a periportal lymph node.

CASE 2.—A white woman, aged 27, with an illness of six days' duration, had an attack of tonsillitis on May 14, 1932, from which she recovered. She felt well until June 6, when an abscess at the root of the right lower canine developed which necessitated extraction of this tooth. Because of pain and swelling, the site of extraction was lanced the following day, and the lesion improved. During the night from June 11 to 12 the patient experienced severe, cramplike abdominal pains centering about the umbilicus. A physician diagnosed the condition appendicitis, and an ice bag was applied which relieved the pains. The next evening

she complained of a slight soreness of her throat which, during the next two days, became severe and was accompanied by high fever, dysphagia, insomnia and choking sensations. Although the throat culture did not show any diphtheria bacilli, 10,000 units of diphtheria antitoxin was given subcutaneously. The patient entered the hospital on June 15. On admission the tonsils were found covered by necrotic membranes, the tongue was coated, and the uvula was markedly edematous. Smear from the tonsils revealed many spirochetes and fusiform bacilli. The temperature remained around 103 F. The blood picture showed: hemoglobin, 85 per cent; erythrocytes, 4,500,000; white cells, 150; lymphocytes, 70 per cent; monocytes, 30 per cent; platelets, 250,000. The patient died two days after admission.

The pathologic anatomic diagnosis was: gangrenous tonsillitis, pharyngitis and glossitis; marked edema of the larynx; a recent tracheotomy wound with aspirated blood in the trachea and main bronchi; fatty changes of the liver; infectious softening of the spleen (weight, 160 Gm.), and parenchymatous degeneration of the myocardium and the kidneys.

Macroscopically, the bone marrow of the femur was moderately firm and purple red with single purple-brown and light yellow areas. Microscopically, about 52 per cent of the marrow was cellular, the remaining part being made up of fat tissue.

The cells were composed of 48.8 per cent of large elements with an ample homogenous or finely vacuolated cytoplasm (fig. 2). The outlines of these cells were irregular with pseudopodia-like protrusions. With azure II-methylthionine chloride the cytoplasm stained from light blue to bluish gray with a light pink hue near the nucleus. The nuclei were oval or bean-shaped and contained a sharply defined chromatin structure. Namely, there were large and small granules which were connected by fine threads. The nucleoli were indistinct and appeared pale pink. A few of these cells showed mitotic division of the nucleus. The chromosomes were short and plump and irregularly arranged. After a long search, a single cell was discovered which contained a fine, purple-pink granulation. In addition to the cells described, there were 10.6 per cent plasma cells, some of which were large with two nuclei, 10.6 per cent erythroblasts, 15.2 per cent normoblasts, 2.6 per cent megakaryocytes, 1.2 per cent megakaryoblasts and 11 per cent lymphocytes. Besides the loosely scattered lymphocytes, single small lymph follicles were found. The picture of the bone marrow of the rib was similar except that the cellularity amounted to 74 per cent.

The pulp of the spleen was rich in plasma cells which often formed small colonies with mitotic figures. There were also many free histiocytes, some of which contained red blood cells. The oxidase reaction failed to demonstrate a single granulocyte. The Kupffer cells of the liver were much swollen and often mobilized. The lymph nodes showed marked erythrophagocytosis by the proliferated sinus endothelial cells, and many plasma cells in the cords of the medulla. Underneath the thick necrotic membranes of the pharynx there was an edematous zone with deposits of fibrin. The zone was loosely infiltrated by small round cells and large free histiocytes with an ample vacuolated cytoplasm and small kidney-shaped nuclei. The adventitial cells of the blood vessels were much swollen and proliferated, and their cytoplasm was deeply basophilic.

CASE 3.—A white woman, aged 24, with an illness of fourteen days' duration, had two teeth extracted on April 12, 1932. Two days later a constant pain in her jaw developed. She also noticed a tender nodule on the left side of the neck, and her throat felt sore. Swallowing was painful, and she felt hot and chilly at times. She entered the hospital on April 27. Her throat was inflamed,

and the cervical lymph nodes of the left side of the neck were swollen. The temperature ranged from 103 to 105 F. Two days later, the tonsils and tonsillar pillars were found covered by a foul-smelling, dirty gray membrane. Two days prior to her death a profuse diarrhea with severe abdominal pains developed. In spite of various therapeutic measures such as blood transfusions, roentgen therapy to the long bones, fresh bone marrow by mouth and intravenous injections of a solution resulting from the action of iodine on sodium carbonate solution, the patient died on May 7. Blood culture showed a pure growth of *Staphylococcus*



Fig. 2 (case 2).—Bone marrow. The myelocytes have lost their granulation and in the nuclei the chromatin is separated into irregular granules. There are several plasma cells and a degenerated megakaryocyte in the field. Technic and magnification same as in figure 1.

albus. The blood picture showed: hemoglobin, 70 per cent; erythrocytes, 3,249,000; white cells, 800; lymphocytes, 89 per cent; monocytes, 9 per cent; irritation forms, 2 per cent, and platelets, 340,000.

The pathologic anatomic diagnosis was: gangrenous tonsillitis; pseudomembranous esophagitis; gangrenous ulcerative enteritis and colitis; hyperplasia of the cervical, mesenteric and axillary lymph nodes; moderate fatty degeneration of the myocardium, liver and kidneys; hyperplasia of the spleen (weight, 318 Gm.); slight fibroplastic deformity of the mitral valve, and focal myocardial fibrosis.

On gross examination the bone marrow of the femur was soft and reddish brown. Microscopically, 62 per cent of the marrow was made up of dense accumulations of cells. The capillaries were much engorged with blood.

Similar to the bone marrow in the second case, there were numerous large lymphoid cells with a basophilic vacuolated cytoplasm and coarsely granular nuclei. The cells contained no granules and did not give the oxidase reaction. Their percentage amounted to 29. The most striking feature, however, was the great number of megakaryocytes (8.6 per cent mature forms and 22 per cent megakaryoblasts). About half of the megakaryocytes were well preserved (fig. 3 A), while the other half showed different stages of degeneration with karyolysis which terminated in complete necrosis (fig. 3 B). The megakaryoblasts were intact and often were found in mitotic division with large chromosomes. There were 36 per cent erythroblasts, 3.6 per cent normoblasts, 27.2 per cent lymphocytes,

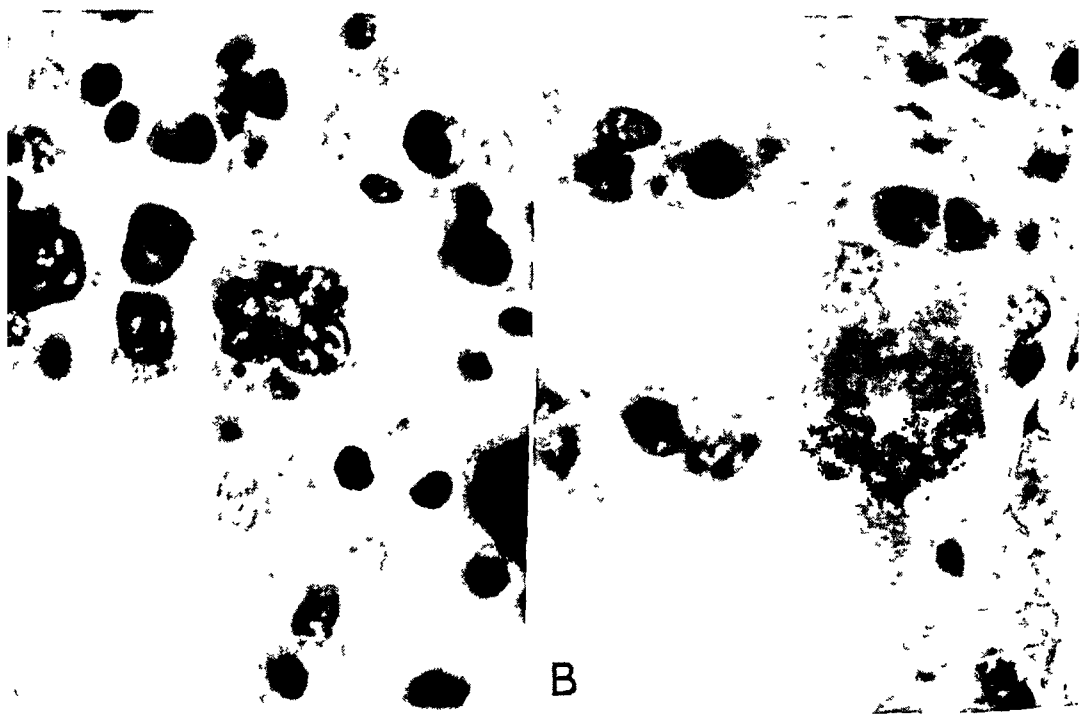


Fig. 3 (case 3).—Bone marrow showing: A, well preserved megakaryocytes; B, necrotic megakaryocyte. Technic and magnification same as in figure 1.

22.8 per cent plasma cells and 3 per cent free histiocytes. Between these different types of cells a fine net of fibrin could be demonstrated, and there were many recent extravasations of blood. The histologic picture of the bone marrow of the rib was similar except that the megakaryocytes formed 15 per cent of the cells, and nucleated red cells were fewer.

In the spleen a diffuse thickening of the reticulum was found. The endothelial cells of the sinusoids and the reticular cells of the cords of the pulp were swollen, and the pulp contained many plasma cells and a few normoblasts. Not a single granulocyte could be detected. In the lymph nodes, too, the reticulum was thickened, and there was a hyperplasia of the reticulo-endothelial cells. Underneath the necrotic membranes of the esophagus and intestine there was much edema with thrombosis of the blood vessels. The loose connective tissue contained many large, free histiocytes with vacuolated cytoplasm.

CASE 4.—A white woman, aged 43, whose illness was of four weeks' duration, stated that she was well until a month before when her gums became swollen and painful. A week later a sore throat developed which was associated with much cough productive of pus and mucus. The patient had a similar attack in Paris in May, 1929. This time, her condition became progressively worse, and the temperature rose to 102 F. She entered the hospital on Nov. 16, 1929. The right nostril showed an ulceronecrotic lesion. The right tonsil was covered by a thick, adherent dirty gray membrane, and the cervical lymph nodes were slightly swollen. Smears from the right tonsil revealed many diplococci but no spirochetes or fusiform bacilli. The urine contained albumin (3 +) and a few hyaline casts. The blood picture showed: hemoglobin, 75 per cent; erythrocytes, 4,050,000; white cells, 350; lymphocytes, 94 per cent; monocytes, 4 per cent, and neutrophilic leukocytes, 2 per cent. The patient died on November 19.

The pathologic anatomic diagnosis was: gangrenous tonsillitis; ulceration of the skin of the right nostril; slight eccentric hypertrophy of the heart (weight, 330 Gm.); scars in the wall of the left ventricle and a partially organized thrombus about an aberrant tendon cord of the left ventricle; miliary abscesses of the kidney (staphylococci); arteriolosclerosis of the kidneys, liver, spleen and pancreas; recent hemorrhages in the lungs; slight fatty changes of the liver and passive congestion of the spleen (weight, 190 Gm.).

Macroscopically, the marrow of the femur was soft and pale yellow gray. Microscopically, it appeared fatty with scattered islands of cells, some of which were typical lymph follicles. The other islands were composed of the lymphoid cells described in cases 2 and 3 and of erythroblasts and normoblasts. There were a moderate number of well preserved megakaryocytes. A few oxyphilic granulocytes were found after considerable searching. The bone marrow of the vertebral bodies was more cellular than that of the femur. Megakaryocytes were numerous, and there were also many megakaryoblasts. In addition to the cells found in the femur marrow, plasma cells and monocytoïd cell forms were present. The bone marrow of the sternum and the ribs resembled the vertebral marrow. In the ribs the plasma cells were numerous, and fibrin was seen between the cells.

The abscesses in the kidney were formed by histiocytes with small fat globules and by lymphocytes. In the sections stained for oxidase few cells with single granules were seen in the abscesses. There was a moderate activation of the Kupffer cells of the liver and of the reticular cells of the spleen and lymph nodes.

CASE 5.—A white woman, aged 52, with an illness of six days' duration, was well until Dec. 30, 1931, when she experienced severe pains in the rectum during and following defecation. The painful defecation was accompanied by the passage of a large amount of bright red blood. The following day she complained of a sore throat which increased so much in severity that she was unable to swallow. At the same time her neck became swollen. She entered the hospital on Jan. 4, 1932. On the soft palate just superior to the right tonsil there was an irregular ulcer about the size of a dime, the floor of which was black. Both sides of the neck were swollen and tender. Her temperature on admission was 101 F. The urine contained albumin (2 +), a trace of bile and a few pus cells and hyaline casts. The blood culture showed hemolytic staphylococci; the throat culture, staphylococci, *Micrococcus catarrhalis* and *Micrococcus tetragenus*. The blood picture showed: hemoglobin, 70 per cent; erythrocytes, 3,600,000; white cells, 700; lymphocytes, 84 per cent; monocytes, 16 per cent. The patient died fifteen hours after admission to the hospital.

The pathologic anatomic diagnosis was: gangrenous lesions of the mouth, throat, upper lip, skin of the neck and mucocutaneous junction of the rectum and

at the cardia of the stomach; slight fibroplastic deformity of the mitral valve; dilatation of the left cardiac chamber with sclerosis of the endocardium; fatty changes of the liver and kidneys; fibrosis of the splenic pulp (weight of spleen, 170 Gm.) and slight icterus.

The marrow of the femur was light yellow and fatty. It contained single light brown areas which were located chiefly in the periphery. Microscopic examination revealed fat tissue with much congested capillaries. Some of the capillaries were occluded by fibrin, and fibrin was also found between the cells. Scattered between the fat cells there were small accumulations of lymphocytes and of larger lymphoid round cells with a deeply basophilic cytoplasm and round nuclei the chromatin net of which was coarse. Some of these cells were vacuolated, and the content of the vacuoles assumed a light pink color. There were also a few small groups of orthochromatic normoblasts, a moderate number of plasma cells and of monocytoïd elements with bluish-gray cytoplasm and kidney-shaped nuclei, and a few megakaryocytes the nuclei of which either stained diffusely or were broken up into irregular segments. The reticular cells were prominent and contained red blood cells. The adventitial cells of the blood vessels were swollen, and their ample cytoplasm was stained a deep blue.

In the spleen the reticular cells of the pulp were swollen and mobilized, and some of the reticular cells contained red blood cells. The cords harbored a moderate number of plasma cells. The trabeculae were infiltrated by lymphoid round cells which extended to the endothelium of the trabecular veins. The Kupffer cells of the liver and the reticular cells of the lymph nodes were swollen and increased in number. The necrotic lesions in the mouth, throat, neck and rectum were separated from the intact tissue by accumulations of lymphocytes and plasma cells. The capillaries and veins were wide and were often occluded by fibrin or mixed thrombi.

Agranulocytosis Following Antisyphilitic Treatment.—CASE 6.—A Negress, aged 38, with an illness of four weeks' duration, began to feel weak and to have pains in both arms and legs, three and a half weeks before entrance to the hospital. She consulted a physician who, after having found that her blood gave strongly positive Wassermann and Kahn reactions, gave her two injections of neoarsphenamine followed by two injections of mercury oxycyanide. She received a third injection of neoarsphenamine and mercury cyanide. At the time of the first injection her temperature was 101.8 F. After the last injection she had a severe reaction and was advised to go to the hospital. On entrance to the hospital she complained of shortness of breath and diarrhea, with stiffness of the legs and inability to walk. She had had four pregnancies and two miscarriages, the last one nine months before. She admitted taking alcohol to excess. Her temperature was 104 F. She had great difficulty in speaking, and an examination of the throat disclosed several large ulcerated areas in the pharynx and at the base of the tongue. Her neck was very tender. Cultures taken from the throat revealed hemolytic streptococci. The blood picture showed: hemoglobin, 70 per cent; erythrocytes, 3,700,000; white cells, 3,500; lymphocytes, 32.8 per cent; monocytes, 67.2 per cent, and blood platelets, 340,000. The patient died six days after admission.

The pathologic anatomic diagnosis was: gangrenous ulcerative glossitis; ulcerative colpitis; severe parenchymatous degeneration of the myocardium and kidneys; fatty changes of the liver; hypostatic pneumonia in both lower pulmonary lobes and recent fibrinous pleuritis over the left lower lobe; fibrinous pericarditis; infectious softening of the spleen (weight of the spleen, 245 Gm.); nodose goiter, and fibrous adhesions about the ileum, sigmoid colon and both ovaries and tubes.

The marrow of the femur was soft, light yellow-gray mottled with pale purple-red. Microscopically, 70 per cent of the marrow was found to be composed of islands of cells which contained the following types of cells: myeloblasts, 1.2 per cent; neutrophilic myelocytes, 54.2 per cent; neutrophilic leukocytes, 6.4 per cent; eosinophilic myelocytes, 3.4 per cent; eosinophilic leukocytes, 1.4 per cent; erythrogonia, 2.4 per cent; erythroblasts, 6.2 per cent; normoblasts, 17.2 per cent; megakaryoblasts, 0.4 per cent; megakaryocytes, 1 per cent; lymphocytes, 0.2 per cent; plasma cells, 6 per cent. While the myeloblasts appeared well preserved, the neutrophilic myelocytes showed severe changes (fig. 4). The granules were swollen and took the stain poorly. Their outlines were irregular and indistinct, and one obtained the impression that the granules would melt away and would mix with the cytoplasm which was finely vacuolated. In the nuclei the chromatin was separated in the form of large and irregular clumps. Some of the cells were free from granules; their nuclei were either fairly well preserved or pyknotic. There was an occasional mitotic figure in a cell the granules of which were relatively well defined. The mature neutrophilic leukocytes revealed an excessive lobulation of the nuclei and changes of the granules similar to those seen in the myelocytes. In the oxyphilic granulocytes the alteration of the granules was less

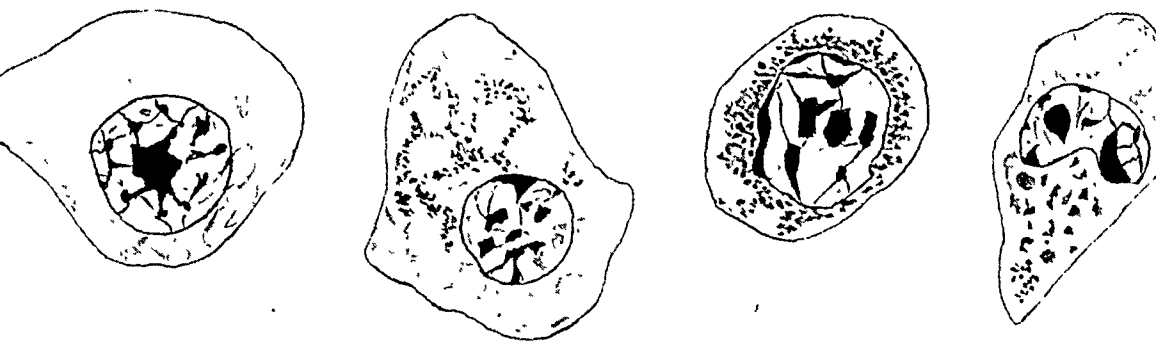


Fig. 4 (case 6).—Ink sketch of the bone marrow showing the gradual disappearance of the granules and the vacuolation of the cytoplasm of the myelocytes. In black and white these changes are difficult to reproduce. Technic same as in figure 1. Magnification, $\times 2,000$.

pronounced; but, in these cells too, the granules were often clumped together and not sharply differentiated from the cytoplasm. The megakaryocytes appeared intact. The normoblasts varied considerably in size, and some of them were large. The reticular cells were swollen, and many of them contained erythrocytes, normoblasts, degenerated granulocytes and pigment granules.

In the pulp of the spleen there were a few neutrophilic myelocytes and leukocytes the granulation of which showed the same changes as those described in the bone marrow. The pulp was rich in plasma cells and free histiocytes, and there were also a few normoblasts. In the liver the Kupffer cells were much swollen, and many free monocytoïd cells were seen in the lumen of the sinusoids. The portal blood vessels contained also single degenerated neutrophilic myelocytes and leukocytes and normoblasts. In the lymph nodes no granulated elements were found. There were much swelling and proliferation of the reticulo-endothelial cells, and the medulla was rich in plasma cells. The necrotic mucosa of the tongue and vagina was not sharply separated from the intact tissue. About the necrosis there were small accumulations of plasma cells, lymphocytes and free histiocytes.

Between these cells a few degenerated neutrophilic leukocytes, fairly well preserved eosinophilic leukocytes and intact mast cells were present.

CASE 7.—A white woman, aged 25, deaf, with an illness of eighteen days' duration, entered the hospital in such a serious condition that the history had to be taken from her husband, who reported that she had been well until two weeks before when a severe chill suddenly developed followed by pain in the chest and cough. The sputum was at first mucopurulent and later became blood-tinted. The husband also stated that for the past two years she had been receiving antisyphilitic treatment. The patient's temperature was 104 F. At the inner side of both nostrils there were several red papules, and the right cheek showed a crusted pustule about 1 cm. in diameter. The gums were discolored and covered by a dirty gray, thin membrane. A few lymph nodes could be palpated on both sides of the neck, and about the anus there were many small cauliflower-like masses (condylomata acuminata). The Wassermann reaction of the blood was two plus. The blood cultures proved to be sterile. The blood picture showed: hemoglobin, 75 per cent; erythrocytes, 3,900,000; white cells, 1,900; lymphocytes, 90 per cent; monocytes, 6 per cent, and irritation forms, 4 per cent. The patient died four days after admission.

The pathologic anatomic diagnosis was: gangrenous and ulcerative tonsillitis and pharyngitis; septic tumor of the spleen (weight of the spleen, 650 Gm.); marked cloudy swelling of the liver and the kidneys; ulcerative colitis and typhilitis; pseudomembranous urethritis; hemorrhagic confluent bronchopneumonia in the right upper lobe; cholelithiasis and chronic cholecystitis, and dried necrotic lesions on the right cheek and about the nostrils.

The marrow of the femur was fatty and light yellow. Histologically, there were only a few small islands of cells between the fat cells which amounted to about 1 per cent. These islands consisted of normoblasts (70 per cent), degenerated neutrophilic myelocytes (15 per cent), degenerated oxyphilic myelocytes (3 per cent), lymphocytes (7 per cent), plasma cells (4 per cent) and free histiocytes (1 per cent). The degenerated neutrophilic myelocytes had completely lost their granulation, the cytoplasm was vacuolated, and the nuclei were often broken up into coarse segments. In the oxyphilic granulocytes the granules stained pale red. Many of the plasma cells had pyknotic nuclei. The bone marrow of the ribs was much more cellular than that of the femur, containing 82 per cent myeloid cells, chiefly erythroblasts and normoblasts. The neutrophilic myelocytes appeared better preserved, but only a few of them showed an intact granulation. There were many well preserved young and mature megakaryocytes and megakaryoblasts which formed small groups and were equal in number to the myelocytes.

Outside the bone marrow no granulocytes could be found. The pulp of the spleen contained a few young and mature megakaryocytes and many free histiocytes. The medulla of the lymph nodes was rich in plasma cells. The defense reactions against the ulcerative and necrotic lesions in the pharynx and colon consisted of accumulations of lymphocytes, plasma cells and large, free histiocytes with a vacuolated cytoplasm.

Prolonged Septicemia (Sepsis Lenta) with Agranulocytosis.—CASE 8.—A white woman, aged 42, for the past five years had been suffering from frequent attacks of arthritis which, during the last year, became more severe, causing a moderate deformity of the fingers and wrists. Four months before the present illness the patient was in the hospital with a definite attack of cardiac decompensation. Her condition improved, and she went home but returned two months later with

erysipelas of the face. She recovered from the erysipelas, but had several "sinking spells," which she attributed to her heart. Two days before readmission to the hospital she experienced a severe chill followed by many less severe ones. In the last few months she had lost 30 pounds (13.6 Kg.). On admission, the temperature was 105.6 F. The pulse rate was 136, and the respiratory rate 26. The mouth could be opened only with difficulty because of a marked injection of the throat. The tonsils and the posterior wall of the pharynx were covered by a dirty yellow-gray membrane which bled on removal. There was also a marked tenderness and swelling at the right angle of the jaw. The heart was slightly enlarged and a faint systolic blow was heard at the apex. The spleen was distinctly enlarged and the fingers and wrists were much deformed. The blood picture showed: hemoglobin, 35 per cent; erythrocytes, 1,480,000; white blood cells, 600; lymphocytes, 81 per cent; monocytes, 17 per cent; irritation forms, 2 per cent; platelets, 42,000; bleeding time, four and one-half minutes; coagulation time, eighteen minutes. The blood culture showed *Streptococcus viridans*. (A blood culture taken at home, a month prior to entrance to the hospital, had also shown green streptococci.) The throat culture showed green and hemolytic streptococci. Soon after admission the patient lapsed into coma and died two days later.

The pathologic anatomic diagnosis was: pseudomembranous tonsillitis and pharyngitis; sepsis lenta; acute glomerulonephritis; subicteric discoloration of the skin and sclerae; marked chronic hyperplasia of the spleen (weight of the spleen, 620 Gm.); slight hypertrophy of the heart (weight of the heart, 365 Gm.); cloudy swelling of the liver; severe anemia; deforming arthritis of the finger and wrist joints of both hands; nodose goiter, and a hemorrhagic corpus luteum cyst.

Cultures taken from the spleen yielded green and hemolytic streptococci.

The bone marrow of the femur was soft and dark purple-gray. On microscopic examination the marrow was found much congested, and the reticular cells were markedly swollen and contained many red blood cells. The cell content amounted to 80 per cent. The following cell forms could be distinguished: myeloblasts, 0.2 per cent, and neutrophilic myelocytes, 2 per cent. These cells revealed severe degenerative changes or were completely necrotic. The nucleus was often fairly well preserved (except for the necrotic cells in which no nucleus could be seen). The outlines of the cells were irregular, and the cytoplasm was finely vacuolated, some of the vacuoles staining a light pink. The specific granules were scanty. There were 4 per cent erythrogonia, 20 per cent erythroblasts and 49.5 per cent normoblasts. Among the normoblasts there were single large forms. Examination also disclosed 7 per cent lymphocytes, 3.6 per cent plasma cells, 5.6 per cent monocytoïd cells, 2 per cent free histiocytes, 2 per cent megakaryoblasts and 4 per cent megakaryocytes. The megakaryocytes revealed degenerative changes, and some of them were necrotic. In addition to the diffusely scattered lymphocytes, there were many well defined lymph follicles.

In the myocardium typical Aschoff bodies with fibrinoid necrotic center and mononucleated and multinucleated myocytes in fan-shaped arrangement were found. The heart valves were microscopically unchanged. The spleen showed a thickening of the reticulum, much erythrophagocytosis by the reticular cells and many plasma cells and single nucleated red blood cells. In the liver the Kupffer cells were prominent, and the capillaries contained many free histiocytes.

CASE 9.—A Negro, aged 52, stated that for the past year he had noted a progressive enlargement and pain, first of his small joints, and then of his large joints. The symptoms gradually spread from the finger joints to the wrist, knee, hip and lumbar joints until practically all the joints were involved. There was a slight remission up to two months before admission to the hospital when the

symptoms became exaggerated, so much so that the patient had to remain in bed and was unable to move. During the last ten months he had lost 45 pounds (20.4 Kg.). He was a heavy drinker, consuming half a pint of whisky a day for two years. On admission his temperature was normal, but during his four weeks' stay in the hospital he had a remittent fever up to 101 F. Examination of the lung and heart gave negative results, and the spleen was not palpable. The essential observations were a marked muscular atrophy with tenderness and limitation of motion. The finger joints were deformed. The Wassermann reaction was negative. The blood picture showed: hemoglobin, 65 per cent; erythrocytes, 3,600,000; white cells, 1,800, and lymphocytes, 82 per cent. The majority of the lymphocytes were larger than the normal small lymphocytes and possessed an ample light blue cytoplasm with scanty azure granules. There were 18 per cent. monocytes. While in the hospital the patient had several attacks of sore throat.

The pathologic anatomic diagnosis was: sepsis lenta; moderate generalized anemia; moderate jaundice; deforming arthritis of the fingers, wrists, toes and knees; slight induration of the spleen (weight of the spleen, 150 Gm.); brown atrophy of the heart (weight of the heart, 260 Gm.); fibrous obliteration of the pericardial sac; slight atrophy of the liver; chronic peptic ulcer of the duodenum, and diffuse colloid goiter.

Cultures taken from the heart's blood revealed a pure growth of green streptococci.

The bone marrow of the femur was moderately firm and yellow-gray with purple gray areas. Microscopically, four fifths of it consisted of fat tissue, the rest being formed of myeloid cells. The reticular cells were filled with iron pigment. There were 22 per cent myeloblasts and 22.6 per cent neutrophilic myelocytes. The nuclei of the myelocytes were broken up into coarse chromatin granules. The specific granules were transformed into rose red droplets which seemed to fuse with the pale stained cytoplasm. There were 6.8 per cent neutrophilic granulocytes the granulation of which was indistinct. There were eosinophilic myelocytes (1.4 per cent), eosinophilic leukocytes (0.6 per cent) and basophilic myelocytes (1 per cent). These cells showed a fairly intact granulation. Examination also showed 1.2 per cent erythrogonia, 6.8 per cent-erythroblasts, 31.4 per cent normoblasts, 3.6 per cent lymphocytes, 8.8 per cent plasma cells, 12.4 per cent monocytoïd cells and 1.2 per cent megakaryocytes.

In the myocardium there were small perivascular accumulations of lymphocytes. The reticular cells of the spleen were filled by erythrocytes and iron pigment, and the cords of the pulp contained many plasma cells and free histiocytes. After a long search, a few neutrophilic leukocytes were found. The liver showed areas of extreme dilatation of the sinusoids in which the Kupffer cells were swollen and proliferated and formed small nests. The periportal tissue was infiltrated by lymphocytes and plasma cells, and there were also a few well preserved oxyphilic leukocytes. The lymph nodes revealed swelling and proliferation of the reticular endothelial cells and much erythrophagocytosis by these cells. In the medulla many plasma cells were present.

COMMENT

In three of the cases of apparently idiopathic agranulocytosis and in one of the cases in which the history suggested relations between the agranulocytosis and antisyphilitic treatment, the bone marrow of the femur was found to be much more cellular than the age of the patients would lead one to expect. In this hyperplasia the granulopoietic tissue

took an active part, and it seems, therefore, that in some instances the agranulocytic catastrophe is preceded by proliferation of the young myelocytes. In the remaining cases the cell content of the bone marrow of the femur was not increased, and the destruction of the granulopoietic tissue did not follow an initial hyperplasia.

In both the hyperplastic and the nonhyperplastic bone marrow the granulopoietic cells revealed severe regressive changes, and it was often only by comparison with the less altered cells that the young myelocytes could be identified as such. Correlating the histologic changes in the different cases, I have obtained the impression that the specific granulation is the first to become affected while the nucleus remains intact for some time and may even divide by mitosis. The specific granules swell, their outlines become indistinct, and small vacuoles often appear around them. The granules later dissolve into these vacuoles, and pale, purple-pink droplets result which fuse together giving a vacuolated appearance to the cells. In the meantime the chromatin of the nuclei has become separated into coarse, sharply defined clumps, and the nucleoli have disappeared. An occasional mitosis may be detected in a cell which has been deprived of its granulation. The mitoses are, however, atypical, with short and clumsy chromosomes, and I think that they do not pass beyond the metaphase. Finally, the nucleus shrinks and disappears, the cytoplasm coagulates and the cell is dead. With the dissolution of the granules into the vacuoles, the oxidase reaction becomes negative. When present, the myeloblasts appear intact, which suggests that therapeutic attempts are not absolutely hopeless even in the acute forms of the disease.

I did not have the opportunity to study the bone marrow in a case of agranulocytosis in which the granulopoietic tissue proved to be intact. The explanations which Reichenbach, Zikowsky and Fitz-Hugh and Krumbhaar offered for these cases sound logical, since it is possible that disturbances in the maturation of the myelocytes or emigration of the mature granulocytes may precede visible changes in the structure of these cells. In this connection, it may be recalled that hyperplasia of the bone marrow has also been found occasionally in cases of aplastic anemia (Gerlach³¹ and others). But besides lack of maturation or blockade of the bone marrow, a disproportion between destruction of the mature forms and the supply of new cells has to be taken into consideration. Kracke³² believes that the bone marrow is affected before the granulocytes disappear from the blood stream. He and Roberts assume with Weiskotten³³ that the normal span of life of a neutrophilic leukocyte is only four days. Whether this holds true for human leuko-

31. Gerlach, W.: *München. med. Wchnschr.* **79**:1101, 1932.

32. Kracke, R. R.: *J. Lab. & Clin. Med.* **17**:993, 1932.

33. Weiskotten, H. C.: *Am. J. Path.* **6**:183, 1930.

cytes remains to be proved. Since the first description of agranulocytosis by Werner Schultz, interest has been focused on the bone marrow, and Naegeli stressed only severe pathologic changes in the nuclei, cytoplasm and granulation of the neutrophilic leukocytes.^{33a} I fully agree with Naegeli that the few neutrophilic leukocytes which are occasionally found in the blood films in agranulocytosis are most severely altered. In hemolytic anemia the erythropoietic tissue is most active, and yet the number of the erythrocytes in the peripheral blood is much diminished. Excessive destruction of the erythrocytes can be gaged by the hemosiderosis of the blood-forming organs and by the elimination of the iron and other products of the erythrocyte cleavage. The destruction of the leukocytes does not lead to microscopically visible waste products, but the study of the uric acid metabolism of subjects on a purine-free diet allows certain conclusions as to the extent of leukocytic disintegration (see the interesting studies of Krainick³⁴ on cases of myelosis). I suggest that such studies be made in cases of agranulocytosis.

The great majority of the cases of agranulocytosis show histologic evidences of a severe injury to the granulopoietic tissue. One may question the significance of the granulolytic processes which I have put in the foreground of my histologic description, and one may consider them as artefacts due to postmortem changes. Undoubtedly a biopsy on bone marrow during life is superior to examination of the bone marrow removed at autopsy (Custer,³⁵ Dameshek and Ingall and others). The method of biopsy, however, has its limitations. Some investigators will hesitate to perform even a small operation in a case of agranulocytosis, since extensive necrosis of the skin has been observed following the needle wounds made in puncturing the veins of the arms. The small bit of tissue removed from the sternum will hardly allow definite conclusions as to the condition of the bone marrow in general. In case 7, for instance, there was a considerable difference between the bone marrow of the ribs and that of the femur. Furthermore, biopsies necessitate decalcification.

In the majority of the cases on which my studies were based, especially in those in which the pictures were taken, the autopsy was performed within three hours after death. The greatest care was taken in fixing the marrow, and in preparing the sections and the other bone marrow elements, in particular the delicate myeloblasts, hematogonias

33a. In a case of cyclic benign neutropenia, Rutledge and his associates (*Bull. Johns Hopkins Hosp.* **46**:369 [June] 1930) found a marked decrease in motility of the neutrophilic leukocytes associated with a diminished intake of neutral red just before and during the attack.

34. Krainick, H. G.: *Deutsches Arch. f. klin. Med.* **172**:70, 1931.

35. Custer, R. P.: *Am. J. M. Sc.* **185**:617, 1933.

and megakaryoblasts were excellently preserved. When autopsy is performed in cases of septicemia twelve hours or more after death, the granules of the myelocytes often stain poorly or not at all. But there is not the peculiar swelling and dissolution of the granules into vacuoles which I have stressed, and I am therefore inclined to believe that this dissolution is an intravital phenomenon.

In several of my cases the giant cells in the bone marrow were conspicuous. They were increased in number, and many young forms with signs of multiplication were present. Similar observations were made by Koch, Richards, Zikowsky, Hallermann, Petri, Rotter and Uffenorde. It is of particular interest that, besides proliferation, the megakaryocytes often showed evidences of disintegration (fig. 3). Degeneration of the megakaryocytes in cases of agranulocytosis was also described by Rose and Houser, Hartwich, van den Wielen, Zikowsky and others. Hence, in agranulocytosis the alteration is not always restricted to the myelocytes but may involve also the megakaryocytes, which points to transitions to aleukia hemorrhagica (Frank) or thrombopenic granulocytopenia (Kracke).

As far as the erythropoiesis is concerned, a moderate anemia develops usually in cases of more prolonged agranulocytosis (Bock and Wiede³⁶ and others). According to Brogsitter and von Kress,³⁷ this anemia does not assume the character of an aplastic anemia. The bone marrow in typical cases of agranulocytosis shows a normal or increased erythropoiesis, and in two of my cases the erythropoiesis went back to the most immature precursors of the red cells, namely, to the erythrogonia. There were, however, some deviations from the normal erythropoiesis. Thus, the normoblasts varied considerably in size, and some of them were large and hyperchromatic. In one case segmentation of the nucleus started before pyknosis was completed, a phenomenon which I have seen in aplastic anemia.

In all the cases which I observed lymphocytes and plasma cells were present in the bone marrow. The percentage of the lymphocytes varied between 0.2 and 27.2, that of the plasma cells between 3.2 and 22.8. In several cases small lymph follicles were found. The reticulohistiocytic elements of the bone marrow were not strikingly affected. In some cases they were slightly hyperplastic with signs of erythrophagocytosis and with iron pigmentation. Free monocytoïd and histiocytic cells amounted to from 1 to 12.4 per cent. There was occasionally a net of fibrin between the cells, and in one case the bone marrow contained recent extravasations of blood.

36. Bock, H. E., and Wiede, K.: *Folia haemat.* **42**:7, 1930.

37. Brogsitter, A. M., and von Kress, H.: *Virchows Arch. f. path. Anat.* **276**:768, 1930.

Are the changes in the bone marrow in so-called idiopathic or primary agranulocytosis specific? Does the study of the bone marrow support the conception that agranulocytosis is a distinct disease entity which should be separated from the symptomatic forms (W. Schultz, Elkeles,³⁸ Friedemann,³⁹ Leon,⁴⁰ Licht and Hartmann, Ottenheimer,⁴¹ Stern,⁴¹ Weiss,⁴¹ Piersol and Steinfield,⁴² Fitz-Hugh and Comroe, Naegeli, Hueper⁴³ and others? I think not. Many cases of agranulocytosis have been observed following antisyphilitic treatment (Farley,⁴⁴ Hartwich, McCarthy and Wilson,⁴⁵ Aubertin and Lévy,⁴⁶ Bock and Wiede and others). Two of my cases apparently belong to this group. The bone marrow in these two cases does not differ from the bone marrow in the idiopathic cases, and I can even go a step further and add that there are no differences between the bone marrow in agranulocytosis and that in neutropenic septicemia. Several years ago I expressed the opinion that agranulocytosis is not a disease but a symptom complex⁴⁷ (see also Zadek, Dameshek and Ingall, Stocké,⁴⁸ Hueber, Rose and Houser, Zikowsky, Hallermann, Reichenbach, Connor, Margolis, Birkeland and Sharp,⁴⁹ Barta and Eroes,⁵⁰ K. Schultz,⁵¹ Uffenorde and others). This conception is also borne out by the morphology of the bone marrow. The agranulocytosis may be caused by a variety of toxic and infectious agents. In producing the symptom complex, a high virulence of the infecting micro-organisms, a specific affinity of chemical substances for the bone marrow, radiating energy, exhaustion of the bone marrow by continuous overstimulation (sepsis lenta) or a congenital weakness of the leukopoietic tissue may be instrumental. The necrotizing gangrenous lesions of the mucous membranes which follow so quickly the disappearance of the granulocytes from the blood stream render etiologic studies exceedingly difficult. A specific agranulocytic virus has not yet been discovered.

38. Elkeles: *Med. Klin.* **20**:1614, 1924.

39. Friedemann, V.: *Med. Klin.* **19**:1357, 1923.

40. Leon, A.: *Deutsches Arch. klin. Med.* **143**:118, 1923.

41. Cited by Hartwich.¹⁵

42. Piersol, G. M., and Steinfield, E.: *Arch. Int. Med.* **49**:518, 1932.

43. Hueper, W. C.: *Arch. Int. Med.* **42**:893, 1928.

44. Farley, D. L.: *Am. J. M. Sc.* **179**:214, 1930.

45. McCarthy, F. P., and Wilson, R.: *J. A. M. A.* **99**:1557, 1932.

46. Aubertin, C., and Lévy, R.: *Ann. de méd.* **27**:151, 1930.

47. Jaffé, R. H.: *München. med. Wchnschr.* **73**:2012, 1926.

48. Stocké, A.: *Folia haemat.* **40**:40, 1930.

49. Connor, H. M.; Margolis, H. M.; Birkeland, J. W., and Sharp, J. E.: *Arch. Int. Med.* **49**:123, 1932.

50. Barta, J., and Eroes, G.: *Virchows Arch. f. path. Anat.* **279**:370, 1930.

51. Schultz, K.: *Beitr. z. path. Anat. u. z. allg. Path.* **89**:350, 1932.

CONCLUSIONS

The histologic changes of the bone marrow in nine cases of agranulocytosis are described in detail. Five of the cases belong to the group of cases of the so-called idiopathic form of agranulocytosis. Two cases seemed to have developed during antisyphilitic treatment, while the remaining two proved to be cases of prolonged *Streptococcus viridans* septicemia.

In agranulocytosis the essential pathologic process is a disintegration of the specific granules of the myelocytes which is followed later by pyknosis of the nucleus and death of the cells. Because of the disappearance of the granulation, the myelocytes lose their characteristic appearance. The degeneration of the myelocytes is sometimes preceded by proliferation.

In a considerable number of cases of agranulocytosis the bone marrow giant cells show signs of proliferation and degeneration which suggest relations to the other forms of regressive blood dyscrasia, in particular to aleukia hemorrhagica.

The changes of the bone marrow in agranulocytosis indicate that agranulocytosis is a symptom complex rather than a disease entity.

CEREBRAL ANEURYSMS

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Forbus¹ recently showed that an absence of media is found at the bifurcation of the cerebral and other arteries. In relation to this study, he presented a case in which there were four small aneurysms at the branching of the cerebral vessels. He found no other vascular lesions, and concluded that the aneurysms were congenital. He believed that such miliary or congenital aneurysms developed at the bifurcation of cerebral arteries in a medial defect. Medial defects of the cerebral arteries have been confirmed by Chase² and Voncken.³ The former reported a large aneurysm at the branching of the middle cerebral artery. Since there were no other vascular lesions, he considered the aneurysms congenital and formed in a medial defect. The cerebral aneurysm reported by Voncken was believed by him to be septic but to originate also in a defect of the media. In the present paper are described six cases of aneurysms of the cerebral arteries in relation to the lesions of the vessels of the circle of Willis and their branches.

REPORT OF CASES

CASE 1.—A woman, aged 39, with a history of hypertension of one and a half years' duration, died after gradually increasing weakness. At necropsy multiple hemorrhages throughout the brain and marked atheromatosis of all cerebral vessels were found. A small vessel in aneurysmal dilatation was observed in the meninges of the cerebellum. A similar one in partial rupture extended along the medulla oblongata and the pons. The entire wall of each vessel was composed of hyalin, while the lumen was almost completely occluded from thrombosis. Similar vessels were observed in the hemorrhages of the brain tissue.

CASE 2.—A man, aged 47, died suddenly in the hospital. For three years prior to death he had been under the care of a physician for double vision, pain in the top of the head, ptosis of the right eye and difficulty in walking. On admission to the hospital the knee jerks were absent, and both eyes showed optic atrophy. At necropsy a ruptured, walnut-sized, thrombosed aneurysm was found extending from the site of the branching of the right internal carotid, middle cerebral, posterior communicating and anterior cerebral arteries to a depression 1 cm. in length on the right side of the pons. Marked atheromatous changes

From the Pathological Laboratory of the Buffalo General Hospital.

1. Forbus, W. D.: Bull. Johns Hopkins Hosp. **47**:239, 1930.

2. Chase, W. H.: J. Path. & Bact. **35**:19, 1932.

3. Voncken, J.: Frankfurt. Ztschr. f. Path. **42**:41, 1931.

were observed in the other cerebral arteries. Microscopic examination of the aneurysm showed complete thrombosis and a narrow wall composed entirely of hyaline tissue.

CASE 3.—A man, aged 83, died following gastro-enterostomy for peptic ulcer. At the branching of the anterior communicating and right anterior cerebral arteries was observed a bean-sized, thrombosed aneurysm. Areas of arteriosclerosis were present in the arteries. On microscopic examination, the aneurysm was found to be at the forking of two vessels. The lesions of the intima of these two vessels varied slightly in extent in different sections of the series. In the sections showing the complete formation of the aneurysm were observed split elastic and collagenous fibers in the intima of one vessel. In the intima of the other vessel was a layered formation of split elastic and collagenous fibers with fat cells in the inner part and hyalin with cholesterol in the outer part. At the formation of the aneurysm from the latter artery were found a few collagenous fibers and hyalin in the medial layer. In the intima of the aneurysm were a few split elastic and collagenous fibers which intermingled with the hyalin and collagen of the media to form one layer. The split elastic fibers increased in number, and then became a single strand a short distance to the formation of the aneurysm from the opposite vessel. From this vessel the wall of the aneurysm extended as a short thin layer of hyalin and a few collagenous fibers. At one place in the wall was a pronounced outer thickening of hyalin and fat cells.

CASE 4.—A man, aged 42, was brought to the hospital after a fall in the street. Death occurred in ten days from bronchopneumonia. At necropsy a ruptured, cherry-sized aneurysm was found at the bifurcation of the left middle cerebral artery. Slight atheromatous changes were present in the other cerebral arteries. The relation of the aneurysm to the bifurcating vessels and to the main vessel differed in the various serial sections. Its formation was essentially similar on both sides. Split elastic and collagenous fibers formed the intima at its formation. The elastic fibers then extended for a short distance as a single layer in the outer part of the thin aneurysmal walls. A few muscle fibers, collagenous fibers and hyalin formed the media, which coalesced abruptly with the intima into a single moderately thick layer of collagenous fibers. Transverse sections of the proximate portion of the aneurysm showed in one place a layered formation of split elastic and collagenous fibers underlying collagenous fibers. The remaining portions of the wall were narrow. In one part were fibroblasts and collagenous fibers; in another, hyalin; and in the rest, varying numbers of collagenous fibers with a single strand of elastic tissue. Both sides of the wall were completely disintegrated at the point of rupture. In some of the serial sections, the intima of both bifurcating vessels of the middle cerebral artery showed extensions to the aneurysm. In the intima of one vessel wall were split elastic and collagenous fibers, while in the other was a layered formation of split elastic and collagenous fibers with an inner layer of collagen, fat cells and fibroblasts.

CASE 5.—A man, aged 28, fell and became unconscious while loading milk into a truck. In the hospital bloody spinal fluid was obtained. After four months of rest he began to work lifting cans and fell with a hemiplegia of the right side. At necropsy, a ruptured, thrombosed aneurysm, the size of a walnut, was found at the first branching of the left middle cerebral artery. No pathologic changes were apparent in any other vessel or organ of the body. Microscopic examination of the aneurysm showed at either side of its formation a splitting of the elastic layer, which continued here and there in the aneurysmal wall as a single layer. The media on one side was gradually replaced by hyaline tissue and collagenous fibers. On the other side, the media ceased abruptly in hyaline tissue

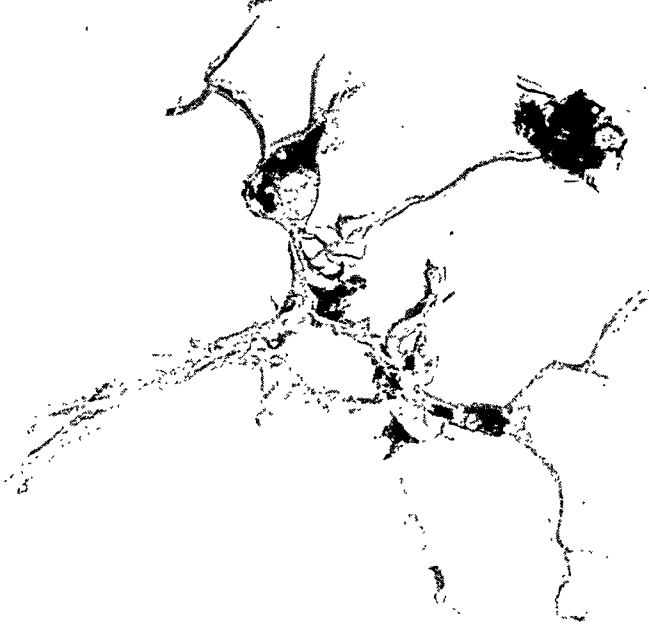


Fig. 1 (case 4).—Ruptured aneurysm in the bifurcation angle of the left middle cerebral artery.

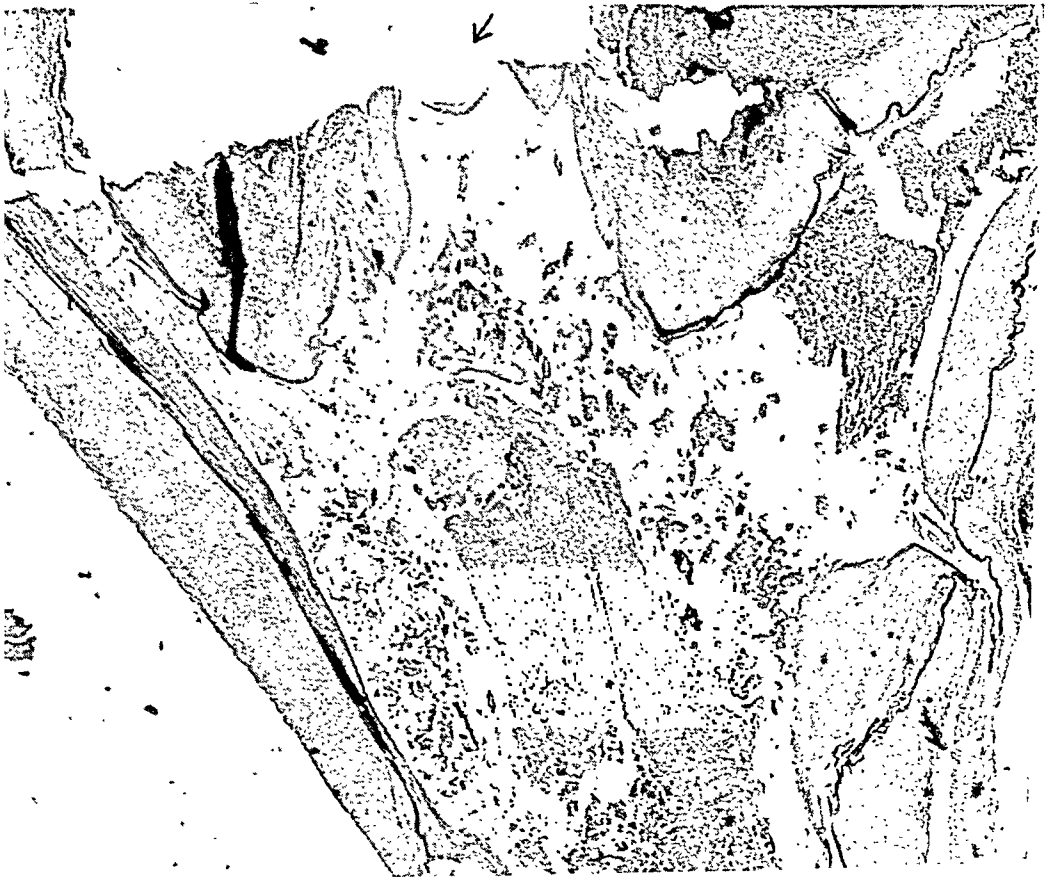


Fig. 2 (case 4).—Formation of an aneurysm in the bifurcation angle. The wall of the aneurysm is partly destroyed.

and then continued as hyalin and collagenous fibers. The intima of the aneurysm was formed of collagen, fat cells, hyalin and cholesterol with granulomatous reaction. The intima and the media gradually formed a single wall of hyaline tissue and collagenous fibers. The adventitia was thickened and showed cellular reaction to previous and present ruptures. The interior of the aneurysm was partially filled with thrombosed blood. The intima of the middle cerebral artery was free from changes except at the formation of the aneurysm, where it became continuous with the inner layer of the aneurysm. The bifurcating artery at the site of the aneurysm showed extensions of collagen and fat cells from the aneurysm. Localized areas of fat absorption were observed at the branching of a small vessel in the basilar artery and at the bifurcation of the right middle cerebral artery. In the other arteries were found an increase in the height and extensions of the areas of split elastic and collagenous fibers at the branchings.

CASE 6.—A man, aged 67, was brought to the hospital in coma. At necropsy a ruptured cherry-sized aneurysm was found at the site of the branching of the left middle cerebral and anterior arteries from the internal carotid artery. The cerebral vessels were thin and smooth except for one small atheromatous area in the basilar artery. Microscopic examination of the aneurysm confirmed its origin in three vessels, which were free from intimal changes except at the formation of the aneurysm. From the intima of one vessel was a short extension of split elastic and collagenous fibers with an inner layer of collagen and fat cells. Both layers terminated in hyaline tissue in which there were no elastic fibers. The media of this vessel ceased abruptly in hyaline tissue which extended for a short distance in the aneurysmal wall. Deeply stained collagenous fibers and fat cells then formed an outer layer to the hyaline tissue of the intima. Extending into the aneurysm from the intima of the other two vessels were collagenous fibers and fat cells which gradually merged into hyaline tissue. The media of these two vessels did not cease abruptly but intermingled with the collagenous fibers. These combined with the intima to form a one-layered growth of hyalin. Split elastic fibers were observed on one side in the outer fat-free collagenous fibers. In the other cerebral vessels not forming the aneurysm was an increase of the split elastic and collagenous fibers in the areas at the branching. The absorption of fat was localized in the macroscopic area at a small branch of the basilar artery.

The cerebral vessels of the six patients with aneurysms and the cerebral vessels of fifty other persons were examined for medial defects. An absence of media was observed at the branching of many small cerebral vessels and at the bifurcation of many large ones. Such absences of media at the bifurcations were observed only once when the muscle fibers in both vessels ran parallel to the elastic layer. They were present when the muscle fibers at the bifurcation were either at right angles or longitudinal to the elastic layer. At all absences of the media the direction of the muscle fibers differed on either side of the omission. Also, the media was never entirely absent. In some serial sections part of the muscle was always present in the defects. An absence of media was frequently observed, not at the branching or bifurcation, but in the wall of a vessel in longitudinal section. At many branches split elastic fibers were seen to spread over and conceal the media. Occasionally split elastic fibers stretched across the media, so that it was loosened from the vessel and gave an appearance of

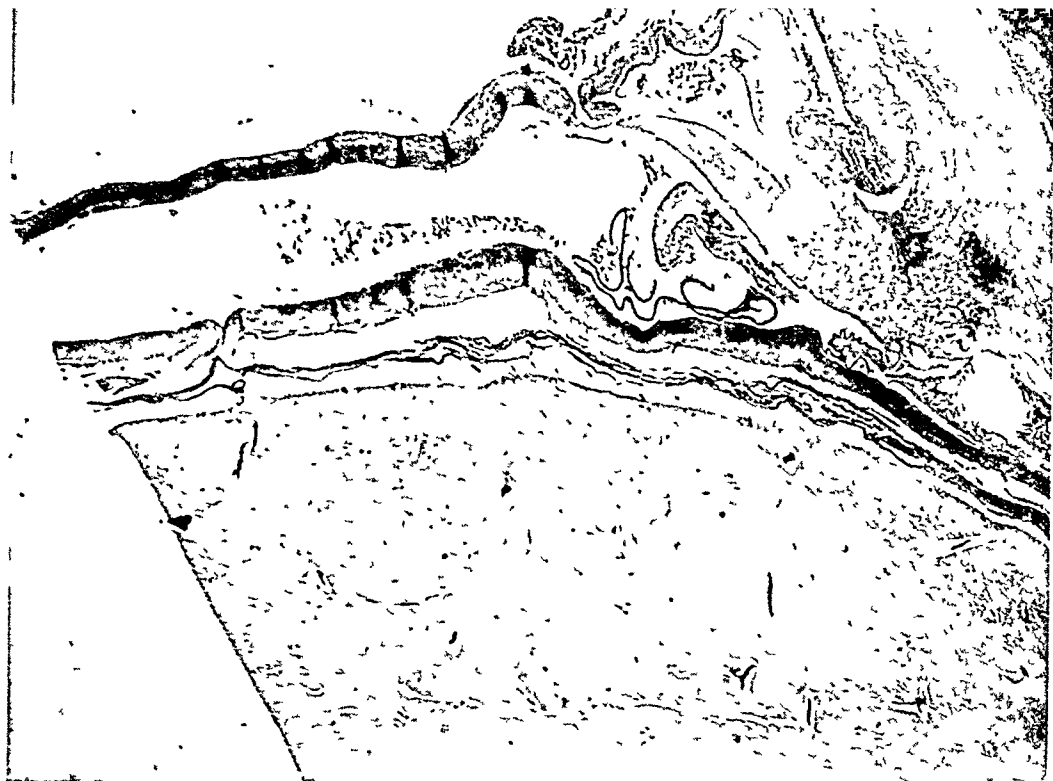


Fig. 3 (case 5).—Absence of arteriosclerosis in the intima of a vessel forming an aneurysm.

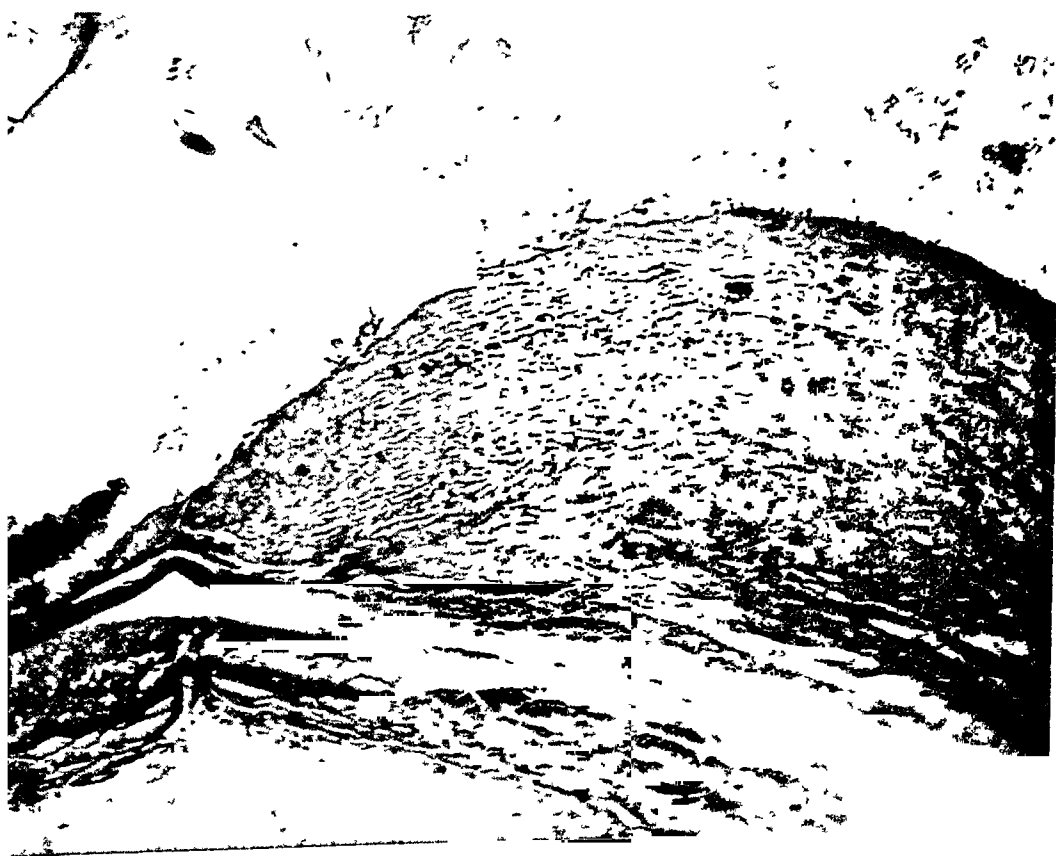


Fig. 4 (case 5).—Absorption of fat in an area of split elastic and collagenous fibers at the branching of a cerebral vessel.

being absent. At many branches and bifurcations the media projected at a sharp angle into the lumen, producing bizarre shapes. Split elastic fibers were spread in and around such projections and so cut across them that medial defects were obtained. At many small branches split elastic fibers so covered the media that they appeared to resemble an aneurysm in early formation. The split elastic fibers at some branchings were fragmented and granular, but in further serial sections these fibers became part of the usual area of split elastic and collagenous fibers at the branching.

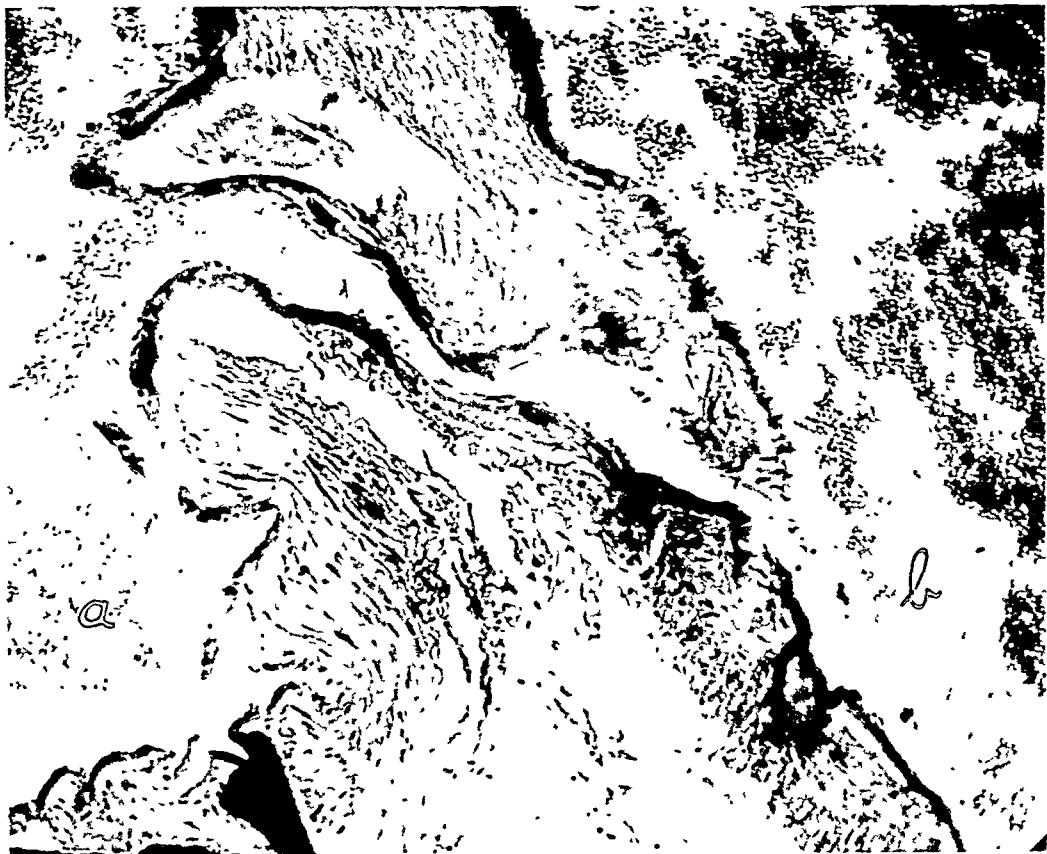


Fig. 5.—Medial defects at the sharp bifurcation of vessels *a* and *b*. There is an apparently artificial loosening of the bifurcation angle as shown by absence of blood cells in intervening space. Nuclei of muscle fibers are seen taking different directions on either side the defect.

COMMENT

Forbus¹ distinguishes a congenital aneurysm from an arteriosclerotic one by the absence of intimal changes in the wall of the vessel from which the aneurysm springs and by the size and location of the aneurysm. Such an aneurysm is small and is situated in the fork of bifurcating vessels. The aneurysm in case 4 in the present series was small and was formed in the center of the bifurcation of the left middle

cerebral artery and would, therefore, appear to be congenital. However, the intima of the bifurcating vessels showed arteriosclerosis, and furthermore these intimal changes were found to unite to the wall of the aneurysm in different sections of the series, suggesting that the aneurysm is not congenital but arteriosclerotic. The aneurysm in case 3 was also similar to a congenital aneurysm, since it was small and was located in the angle of branching vessels. The intima of these two vessels showed old and fresh arteriosclerotic changes which intimate an arteriosclerotic origin of the aneurysm.

If the relation of arteriosclerosis to an aneurysm is established by the change in the intima of the vessels from which the aneurysm arises, in all the presented cases the aneurysms are arteriosclerotic except in cases 5 and 6. In these two cases the vessels forming the aneurysm were free from arteriosclerosis. However, the wall of the aneurysm in the fifth case showed the typical arteriosclerotic growth of collagenous fibers, fat cells, hyalin and cholesterol. The areas of two-layered formation, with hyalin in the outer part and collagen with fat cells in the inner, show that a regressive change from collagen and fat to hyalin takes place as in arteriosclerosis. The wall of the aneurysm in case 6 was similar to that in case 5, except that split elastic fibers were found in the collagenous fibers which were free from fat cells. The walls of these two aneurysms were essentially similar in formation to those in cases 3 and 4. In cases 1 and 2, the aneurysms were composed entirely of hyalin, but hyalin was also present in the other four cases. Forbus¹ believes, however, that the cellular growth in the wall of an aneurysm is not of arteriosclerotic type. He stated that in arteriosclerosis the splitting of the elastic tissue is the final change, whereas in the aneurysm diffuse degeneration and segmentation of the elastic tissue is found underlying intimal thickenings. A study of the elastic tissue in arteriosclerosis shows that the split elastic fibers follow the growth of the collagenous fibers, except when there is a simultaneous growth of fibroblasts, fat cells and collagen. Elastic fibers do not develop in such formations since the absorption of fat tends to destroy collagenous fibers. If fat is absorbed in the split elastic and collagenous fibers, both are destroyed. If split elastic fibers are present in the final arteriosclerotic process, it is because collagenous fibers without fat cells are still present. Their absence in such hyaline tissue or calcium is due either to previous destruction from the absorption of fat or to an inability to develop because the collagenous fibers were quickly destroyed by fat cells. Therefore, the absence or presence of split elastic fibers is determined by the type of arteriosclerotic growth. This appears to be true also of aneurysms, since elastic fibers are absent in hyalin and in collagenous fibers with fat cells but present in fat-free collagenous tissue.

Although Forbus² did not describe elastic fibers as occurring in the congenital aneurysms that he observed, one of which had a wall composed entirely of hyalin, the congenital aneurysm recorded by Duguid⁴ was formed only of elastic and fibrous tissue. In the congenital aneurysms studied by Chase² and Green⁵ not only were split elastic fibers present but also fibroblasts, calcium, hyalin and fat as in arteriosclerosis. Schmidt⁶ considered eleven of his nineteen aneurysms to be arteriosclerotic, but did not make any distinction in the formation of the walls between an arteriosclerotic aneurysm and those he believed to be congenital. Kerpola⁷ divided aneurysms into two classes. In one there is a degeneration of the muscle fibers with a continuous unchanged or split elastic layer. In the other, the media either ceases abruptly at the aneurysm or gradually loses muscle fibers. The intima of the latter group is formed of fibroblastic and split elastic growth which changes into hyalin with a loss of the elastic fibers. He believed that all his cases were arteriosclerotic and suggested that the first change toward the formation of aneurysm is in the media. It is evident that aneurysms are similar in formation, and that they are found in different stages of the same process, which is similar to the intimal growth of arteriosclerosis. The distinction between an arteriosclerotic and a congenital aneurysm cannot, therefore, be made from the formation of the wall.

Although the walls of the aneurysms in cases 5 and 6 were similar to the walls of an arteriosclerotic aneurysm, the absence of arteriosclerosis in the intima of the vessels forming the aneurysm suggests another origin. However, in the cerebral vessel in case 6 was a localized area of fat absorption at the branching of a vessel, while the normally present⁸ areas of split elastic and collagenous fibers at the other branches showed a hyperplastic change. Fat was absorbed in several areas at the branching in case 5, while hyperplastic areas were found at the other branches. Since the aneurysms were found at the branching of the vessels, it seems possible that localized absorption of fat occurred in the areas of split elastic and collagenous fibers at these branchings, and that the aneurysms were formed in relation to these arteriosclerotic areas. Schmidt⁶ commented on the possibility of a localized arteriosclerosis. Furthermore, the occurrence of arteriosclerotic aneurysms at the branching of the cerebral vessels has been described by Wallesch⁹ and others.

4. Duguid, J. B.: *J. Path. & Bact.* **28**:389, 1925.

5. Green, F. H. K.: *Quart. J. Med.* **21**:419, 1928.

6. Schmidt, M.: *Brain* **53**:49, 1931.

7. Kerpola, W.: *Arb. a. d. path. Inst. d. Univ. Helsingfors* **2**:115, 1919.

8. Tuthill, C. R.: *Arch. Neurol. & Psychiat.* **26**:268, 1931.

9. Wallesch, E.: *Virchows Arch. f. path. Anat.* **251**:107, 1924.

A multiplicity of aneurysms also does not distinguish arteriosclerotic from congenital aneurysms, since small multiple arteriosclerotic aneurysms have been reported by McCordock.¹⁰

Neither the formation of the wall of the aneurysm nor the absence of intimal changes in the vessels forming the aneurysm, nor the size



Fig. 6.—*A*, split elastic fibers covering the media at the branching of the vessel; *B*, undercurving of the media and twisting of the vessel before the branching.

and the location of the aneurysm nor the number of aneurysms can serve in determining whether the origin is congenital or arteriosclerotic.

The aneurysms of the small vessels in the first case showed no sacculations as described by Green¹¹ in small hemorrhages of the brain.

10. McCordock, H. A.: *Bull. Buffalo Gen. Hosp.* 1:87, 1923.

11. Green, F. H. K.: *J. Path. & Bact.* 33:71, 1930.



Fig. 7.—*A*, muscle fibers are not running in similar directions on both sides of the defect. There is artificial segmentation of split elastic fibers: a complete area of split elastic fibers at the branching is shown in the succeeding sections. *B*, muscle fibers are shown running in different directions on either side of the defect. The media is rolled under with the elastic fibers bordering the adventitia.

What appeared to be a sacculated aneurysm occurred at the branching of a vessel, but serial sections showed this to be an aneurysmal dilatation of the vessel.

The relation of an aneurysm to so-called medial defects does not appear to be clear. The number of such defects are numerous in the cerebral vessels of each person. If they offer a place of least resistance to blood pressure, it is surprising that aneurysms are not found early in life and in every person. Since cerebral aneurysms are comparatively rare, it is evident that the formation of aneurysms must be due to some primary vascular change rather than to the presence of medial defects only. Furthermore, the existence of a medial defect is difficult to establish. It is apparent that since the cerebral vessels do not run in a plane surface but over an extremely irregular one, they cannot lie in the same plane when embedded, even though injected. A composite picture is therefore necessary in order to see the complete relation of the vessels to each other. The elasticity of the vessels also causes them to twist and to turn in the process of embedding. A proof of such twisting is the rarity of finding the muscle fibers running in the same direction on both sides of a vessel. Such twistings are most pronounced at the bifurcations where the nuclei of the muscles run in a variety of directions. This variation may be considered a normal relation of the muscle fibers, but since it is not regularly found it cannot be due to the growth of the fibers. The absence of similarly directed nuclei on either side of a medial defect also shows that a twisting of the vessels has taken place. It would seem, therefore, that the effect of the twisting and inclination of the vessels at the bifurcations brings the adventitia forward and the media upward, so that only the adventitia and elastic fibers are left at some places in the serial section. This explanation is strengthened by the fact that in the composite picture of the serial sections the media is never wholly absent. If a vessel is twisted throughout its length, the twisting at some point also produces the same medial defect as that at the branching. When the vessels show only slight curving and inclination at the bifurcation, the muscle fibers of the branching vessels tend to run longitudinally with the elastic layer. At such bifurcations are no so-called medial defects unless the angle of branching is too sharp. In such instances projection of the media into the lumen causes the adventitia to be found at some point between the media of the bifurcating vessels, while the elastic layer usually splits over the media. Such sharp angles may also occur at the bifurcation in twisted vessels. At the branching of the vessels, the media may be doubled under so that the adventitia appears in contact with the elastic layer.

Since the medial defects can be considered artefacts, the full explanation of the formation of an aneurysm must be sought elsewhere. The occurrence of light spots in the media underlying fat absorption in the areas at the branching is evidence that the absorption may extend into the media. Since absorption of hyalin succeeds the accumulation of fat, it is suggested that the presence of hyalin in the media at the site of the formation of an aneurysm offers the conclusion that similar changes have preceded the aneurysm. It would appear that absorption



Fig. 8.—Light areas in the media beneath areas of fat absorption in the intima.

of fat in the media causes a weakness of the wall of the vessel which stimulates collagenous growth between the muscle fibers. As the vessel bulges, the intima is extended by a growth of collagenous fibers and possibly split elastic fibers. The absorption of fat leads to the accumulation of hyalin which eventually forms the entire wall.

CONCLUSION

There have been presented five sacculated aneurysms of the large cerebral vessels, varying from the size of a small bean to that of a walnut. Three aneurysms were located at the branching of the vessels;

one in the bifurcation angle of the anterior cerebral and anterior communicating arteries, and one in the angle of the bifurcation of the middle cerebral artery. Various stages of arteriosclerotic changes were observed in the walls of the aneurysms. In two cases there was an absence of arteriosclerotic growth in the intima of the vessels forming the aneurysm. However, these two aneurysms were considered arteriosclerotic because of the hyperplasia of the areas of split elastic and collagenous fibers at the branching of the other cerebral vessels and because of localized absorption of fat in one or more of these areas. In a sixth case were hyaline aneurysmal dilatations of the small arteries of the meninges and of the brain substance with rupture and small hemorrhages. No distinction could be made between arteriosclerotic aneurysms and congenital ones.

The so-called medial defects at the bifurcation of the vessels are explainable as embedding artefacts because of the irregularity of the vascular bed and the twisting of the vessels from elasticity. It is suggested that the absorption of fat in the media underlying the absorption of fat in an area of split elastic and collagenous fibers at the branching of a vessel is the first stage in the formation of an aneurysm.

EXTRAMEDULLARY HEMATOPOIESIS IN A RETROPERITONEAL TUMOR

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Hematopoietic tissue is not uncommonly found apart from the usual sites, in various organs in association with metaplasia of the bone. Extramedullary hematopoiesis, however, has been recorded as a comparatively rare condition and has been the center of considerable discussion for many years. In 1927, Brannan¹ extensively reviewed the literature on this subject, and reported a number of cases occurring in anemic infants. The following case, which recently came under my observation, is of interest in that a large tumor-like mass containing blood-forming elements is a condition infrequently met with in the adult.

REPORT OF CASE

A woman, aged 64, was in good health until one week before admission, at which time cystitis and left-sided pyelonephritis developed. On admission this condition had almost entirely disappeared. On bimanual examination a large globoid tumor mass displacing the rectum could be felt in the left side of the pelvis. A clinical diagnosis of cyst of the broad ligament was made.

At operation a large tumor was found in the hollow of the sacrum, displacing the rectum and sigmoid anteriorly, the bowel lying taut over the anterior surface of the tumor. The tumor occupied the right leaf of the mesosigmoid and was not visible until the peritoneum was incised and about three-fourths inch (2 cm.) of subperitoneal fat was dissected away. By inserting the fingers between the leaves of the mesentery, an encapsulated tumor mass was easily shelled out. Although it was lightly attached to the soft tissues in the hollow of the sacrum just below the promontory, no bony attachments were present. Very little hemorrhage occurred during the operation, the cavity being packed with paraffin gauze, and the abdomen was closed. The patient made an uneventful recovery and was discharged from the hospital two weeks later.

The gross specimen was a roughly globoid mass measuring 11 by 9 by 6.5 cm. and weighing approximately 250 Gm. It was almost entirely enclosed in a thin, glistening capsule which had been somewhat torn on removal. The latter presented a yellowish-gray, translucent appearance with dark brown areas of mottling beneath. A few delicate fibrous tags were adherent to the capsular surface. The tissue was of soft, rubbery consistency and, unlike normal fat, was quite friable and easily fragmented. The cut surface presented a glistening, fatty appearance and was coarsely mottled with irregular chocolate-brown areas suggesting hemorrhage.

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1. Brannan: Bull. Johns Hopkins Hosp. 41:104, 1927.

Microscopic sections stained with hematoxylin and eosin and by Giemsa's method revealed a striking picture. In general, all the essential characteristics of bone marrow were present. Evidence of active blood formation, both erythroblastic and leukoblastic, was found in varying degree throughout all the sections examined, the histologic picture being almost indistinguishable from that of normal or somewhat hyperplastic bone marrow. The cellular background was composed of healthy adult fat cells, supported here and there by minute amounts of connective tissue and fairly well supplied by small vascular channels. Scattered throughout the meshwork of fatty tissue were varying numbers of cells, many of which could be definitely recognized as immature forms of both the red and the white series. Sections stained by Giemsa's method showed easily recognizable myelocytes of all



Fig. 1.—Gross specimen of retroperitoneal tumor.

three varieties. Eosinophilic myelocytes, the granules of which stood out with great clearness, formed a striking part of the microscopic picture. Sections stained by the oxydase method showed that many of the cells contained indole-blue granules (positive). Of the erythroblastic series, frequent normoblasts in varying stages of development were present throughout the sections. A few of these cells were found to be undergoing mitotic division. Numbers of quite large and very immature cells with rounded nuclei and varying amounts of basophilic nongranular cytoplasm were seen. The degree of differentiation of these forms made histologic identification impossible.

In the more cellular areas, which corresponded in appearance to active bone marrow, numbers of large, multinucleated forms interpreted as megakaryocytes were found. In some localities these were very numerous, as many as eight occurring in a single low power field. However, in many of the sections in which

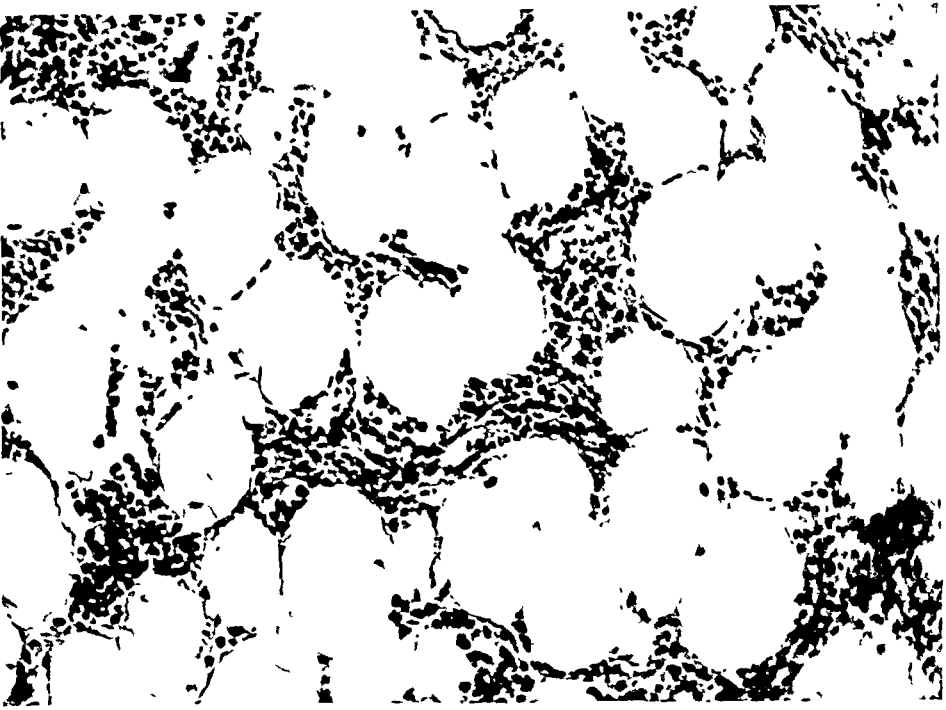


Fig. 2.—The general structure of the tumor, showing its similarity to bone marrow. Groups of blood-forming cells are lying within adipose tissue; $\times 160$.

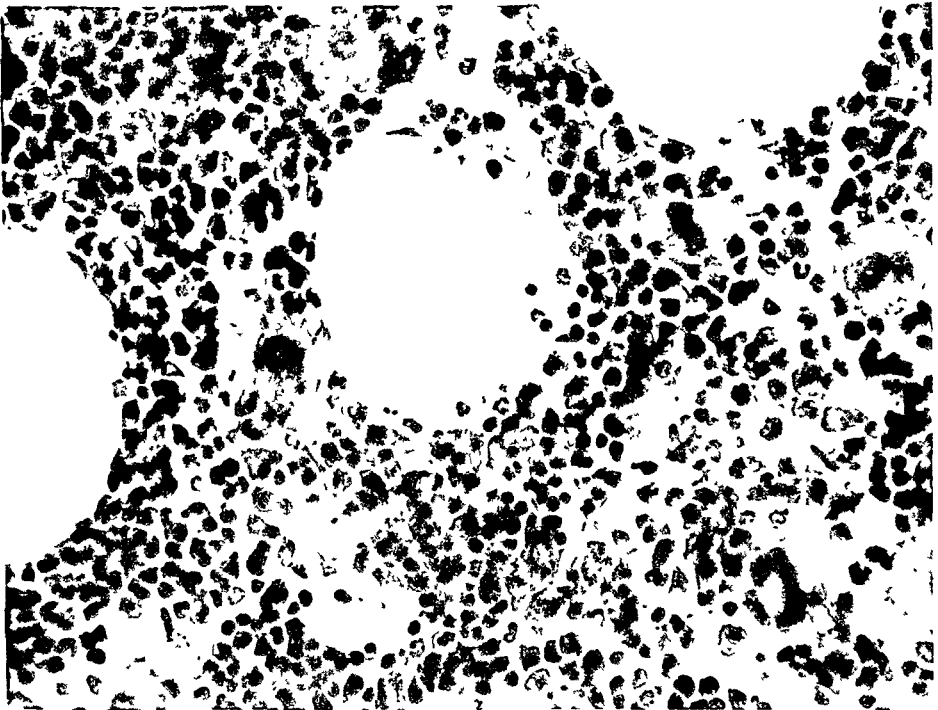


Fig. 3.—A higher magnification, to show more clearly the character of the cells infiltrating the fatty tissue meshwork. The megakaryocytes are quite numerous and prominent in this special region.

hematopoiesis was less active, these cells were met with much less frequently and were often entirely absent.

Varying numbers of red blood cells were found lying between the fat cells, either in association with or entirely apart from areas of blood formation. Throughout the sections considerable activity on the part of the capillary endothelium was observed, with the formation and opening up of many new vascular channels. Small amounts of brownish pigment material which with Perl's stain was found to be iron-containing pointed also to blood destruction taking place to some degree in the tissues. These deposits of hemosiderin were, however, small and scattered, practically all the iron-containing pigment having been phagocytosed by large endothelial cells. Fairly numerous lymphocytes and a few plasma cells were to be seen. In some regions the former were aggregated in small clusters, which did not, however, have the appearance of lymph follicles and did not present germinal centers.

Although the degree of hematopoietic activity varied considerably in different areas, this process was quite apparent in all parts of the tumor examined.

The occurrence of extramedullary blood formation is to be regarded as a purely compensatory mechanism in many cases in which, as the result of destruction, dysfunction or excessive requirements, the bone marrow is unable to meet the demands imposed on it. This is not uncommonly seen where extensive replacement of the marrow by tumor has occurred; Askanazy² has described myeloid changes in the liver and the spleen in such conditions. Similar hematopoietic activity in these and other organs has been noted by several observers in various infectious diseases as well as in pernicious anemia, lead poisoning, chronic nephritis and hemochromatosis. In view of the unusual site in the case just reviewed, the findings of Petri³ are of especial significance. In a series of forty adults, suffering chiefly from acute infections, the majority presented small patches of hematopoietic tissue in the retroperitoneal fat.

Brannan¹ and others have shown that in some of the severe anemias of infants, particularly in the type described by von Jaksch and Luzet, collections of hematopoietic tissue at the renal hili are almost a constant finding, and are also occasionally observed in the liver, spleen, lymph nodes, lungs and dura.

In all the aforementioned cases the formation of blood may be regarded as a compensatory phenomenon. Sometimes, however, it seems that extramedullary blood formation may occur independently of either pathologic conditions of the bone marrow or excessive demands. Saleeby⁴ reported a case in which two small masses of hematopoietic tissue were present in the pleura on either side of the chest of a patient presenting no evidence of anemia. Brannan¹ also found small foci of blood formation in the breasts and in the broad ligaments of infants not suffering from anemia.

2. Askanazy: *Verhandl. d. deutsch. path. Gesellsch.* 7:58, 1904.

3. Petri: *Virchows Arch. f. path. Anat.* 258:37, 1925.

4. Saleeby: *Am. J. Path.* 1:69, 1925.

A review of the literature discloses only three cases similar to that under discussion. Brannan quoted Rich as having found a kidney-sized mass of bone marrow tissue in the thorax of a patient dying of hemolytic jaundice, and Saleeby mentioned a somewhat similar mass occurring in the pleura in a case of osteitis fibrosa cystica. Hofstätter and Schnitzler⁵ discovered a large retroperitoneal tumor in a woman suffering from anemia. This tissue, which showed evidence of blood-forming activity, was attached to, and possibly arose from, the pelvis of the kidney.

The case under discussion offers two important questions for consideration: (1) What is the mode of origin of hematopoietic tissue in this unusual location? and (2) May such a condition be regarded as a compensatory phenomenon? Ziegler, Ribbert and others believed that embolic masses of cells may occasionally be carried by the blood stream from the bone marrow to various parts of the body and set up "metastatic" foci of blood-forming tissue. It has been felt by most observers, however, that these masses arise from remnants of cells and probably represent the sites of embryonic blood formation.

The latter is probably to be looked on as a fairly widespread process, and the possibility of the retroperitoneal fatty tissue being one of the sites in which this occurs must be considered. The observation of Petri³ that blood formation in this locality is a common finding in acute infections lends support to this view. Warren⁶ reported a highly malignant tumor growth having the appearance of bone marrow which he believed originated in the retroperitoneal fatty tissues.

The majority of the cases mentioned in the literature have been associated with anemia of varying degree. The anemia may be regarded as the response to a deficiency on the part of the blood-forming tissues, although isolated instances have been observed in which such a condition did not exist. In the case under discussion the patient suffered from mild secondary anemia. Hematologic examination a few days following operation showed: hemoglobin, 70 per cent; red blood cells, 3,700,000, and white blood cells, 4,300. No apparent cause for the anemia was found. The blood smears showed a normal differential count, with little evidence of variation in the size or the shape of the red cells, a few of which presented slight polychromatophilia. Evidence of active regeneration, however, was found in an increased proportion of reticulocytes, constituting about 7 per cent of the red cells. Although a hematologic investigation was not carried out prior to operation, the amount of blood lost during the procedure could hardly account for the anemia.

5. Hofstätter and Schnitzler: *Arch. f. klin. Chir.* **140**:567, 1926.

6. Warren: *Am. J. Path.* **4**:51, 1928.

In this case it is probable that extramedullary hematopoiesis is not to be regarded as a strictly compensatory mechanism in the sense that the bone marrow was inadequate in the demands for increased production of blood. It seems more likely that, in the presence of slight anemia, tissues still retaining the embryologic potentialities of hematopoiesis responded to the same stimulus which called forth a hyperplasia in the bone marrow.

CONCLUSIONS

A large lipomatous tumor of the retroperitoneal tissues containing all the blood-forming elements of the bone marrow has been described.

As the retroperitoneal fatty tissues probably represent one of the sites of blood formation in the embryo, it is probable that the tumor arose from embryologic cell rests or from tissues still having the potentiality of blood formation.

Under increased functional demands, such tissues will respond to the same stimulus as normal bone marrow and will assume the function of production of blood.

A MALIGNANT NEURINOMA (SCHWANNOMA) WITH EPITHELIAL ELEMENTS

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Tumors arising from peripheral nerves in which epithelial elements were present have been reported by Cohn,¹ Stewart and Copeland² and Masson.³ The presence of such elements is in favor of the point of view that these tumors arise from the sheath of Schwann, which is of ectodermal origin, rather than from the endoneurium or the perineurium, which are mesodermal structures. Nageotte⁴ and Masson³ pointed out the similarities between spontaneously occurring tumors of nerves, experimentally produced schwannomas and regenerating nerves. Verocay⁵ described circumscribed proliferations of Schwann's cells which he believed were the forerunners of these tumors. He stressed the variations in the staining of the fibrils with van Gieson's stain; and Masson also demonstrated that many of them stain differently than true collagenous fibers with trichrome stains. There is considerable evidence which suggests that many of these tumors arise from the neurilemma and that the collagenous-like fibers in these tumors and the endoneurium in normal nerves in part may be formed by the Schwann cells. One can explain the presence of epithelium-like structures in some of these tumors much more readily on the supposition that they arise from the neurilemma rather than from the mesodermal elements.

It is generally agreed that the neurilemma is of neuro-ectodermal origin, as demonstrated by Harrison.⁶ The earlier stages of development of these tumors offer better opportunities for study as to their origin than do later stages, in which, as has been suggested, there may have been a secondary proliferation of connective tissue replacing the neoplastic Schwann cells similar to the replacement of epithelial cells in a scirrhus carcinoma of the stomach.

The case that I shall report is of interest from several angles. Clinically the tumor was of rapid growth, and pain, the chief symptom, was

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1. Cohn, I.: *Arch. Surg.* **17**:117, 1928.

2. Stewart, F. W., and Copeland, M. M.: *Am. J. Cancer* **15**:1325, 1931.

3. Masson, P.: *Am. J. Path.* **8**:367, 1932.

4. Nageotte, J., in Penfield, W.: *Cytology and Cellular Pathology of the Nervous System*, New York, Paul B. Hoeber, Inc., 1932, p. 191.

5. Verocay, J.: *Beitr. z. path. Anat. u. z. allg. Path.* **48**:1, 1910.

6. Harrison, R. G.: *Am. J. Anat.* **5**:121, 1905.

present for five months. Histologically the tumor presented features of a neurogenic sarcoma throughout which there were scattered small masses of epithelial-like cells. Metastases involved the regional lymph nodes and the lungs particularly and were composed of cells like those in the epithelial masses in the primary tumor. Myxomatous degeneration was a marked feature, especially in the central portion of the primary tumor and less so in the metastases.

REPORT OF A CASE

A white man, aged 73, complained of pain in the left thigh and hip of five months' duration. The pain had been more or less continuous and was described as throbbing, occasionally radiating to the leg and ankle. It became increasingly severe. A tumor was not noticed by the patient until several months after the onset of pain, but by the time of admission to the hospital a large mass was palpable in the left thigh. Urinary obstruction developed two weeks before admission, which was relieved by catheterization but recurred four days previous to admission. There was considerable loss of weight during the five months, owing in part to the extreme pain.

Examination showed a man about 75 years of age who was moderately emaciated. The blood pressure was 132 systolic and 84 diastolic, and the heart and lungs were essentially normal. The left thigh was about 4 cm. greater in diameter than the right. In the medial aspect of the proximal half of the left thigh, was a large, movable mass which extended to a point about 17 cm. below the left groin. A soft, semifluctuant area in the central portion of the mass was aspirated, and a gelatinous, slightly blood-tinged material was obtained. This material contained 3.3 per cent albumin, an occasional polymorphonuclear cell and rarer large, irregular cells with deeply stained nuclei and nucleoli. Pressure over the sciatic nerve elicited some pain, but pressure over the tumor was more painful. The prostate gland was slightly large, firm and moderately tender. Roentgenograms revealed slight mottling and increased density in the region of the left hip. Motion of the leg was not limited.

The man continued to lose weight. The tumor increased considerably in size while the patient was in the hospital, and death occurred on the forty-seventh day. A carcinoma of the prostate was suspected clinically.

Necropsy revealed marked emaciation, moderate anemia and slight edema of the subcutaneous tissues of the feet and ankles. The muscles of the lower extremities were equally atrophic. Both testicles were in the scrotum, of equal size, freely movable and free from gross changes on section. Innumerable firm, grayish nodules, from 1 to 15 mm. in diameter, were present in the peripheral portions in all lobes of both lungs; they were most numerous in the lower lobes. Some of the larger nodules were umbilicated. The mucosal lining of the bronchi and larger branches was free from gross change other than a slight hyperemia. The mediastinal lymph nodes revealed only moderate anthracosis. The rectum was displaced toward the right by a tumor protruding into the pelvis on the left side. The rectal mucosa was intact and free from noticeable changes. The prostate was moderately enlarged, uniformly nodular, firm and grayish pink. The left seminal vesicle was surrounded by an increased amount of fibrous tissue. The left iliac lymph glands were enlarged, some being as large as 2 by 3 by 3.5 cm. All except those showing large, yellowish areas of necrosis were firm. In the smaller glands, small grayish areas could be seen in the peripheral portions. The

lower aortic glands were slightly enlarged. The right inguinal and iliac glands were not enlarged.

The tumor in the left thigh measured 10 by 12 by 20 cm.; it was roughly ovoid and slightly lobulated. The proximal third was smaller in diameter and continuous with the mass in the pelvis. The mass was encapsulated and surrounded by stretched adductor muscles that were easily separated from it. The upper portion was fixed by the pelvis, but the lower portion could be moved with the muscles. The pelvic portion was covered by smooth peritoneum. The consistency varied considerably. On section, the softer areas were composed of a structureless, grayish, gelatinoid substance. The firmer areas appeared to consist of intertwining bands of lighter gray with a tendency to whorl formation. Small reddish-brown areas were present in the soft portions. Several small cystlike areas were also present in the more central portions. The pelvic nerves were

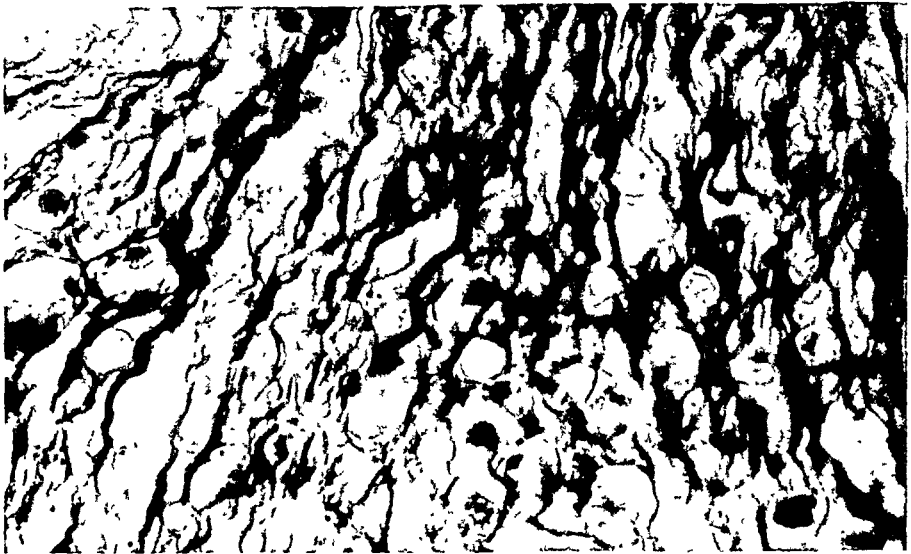


Fig. 1.—Section from an area rich in parallel strands of fibrils of varying caliber. Large cells can be seen between the parallel fibrils which have undergone marked degenerative changes. Laidlaw's silver stain; reduced from a magnification of $\times 2,400$.

not involved except that they were pushed aside by the tumor. The urinary bladder was not involved except for diffuse cystitis. The pelvic bones and the femur were free from gross changes.

Histologic examination of the tumor in the thigh gave rather confusing results, but definitely ruled out certain possibilities. The greater portion was composed of a sarcomatous-appearing stroma presenting features seen in neurogenic sarcomas. Intertwining bundles of elongated fibrils with varying numbers of nuclei, some of which were very much elongated, were seen in the compact areas. Some of these bundles of fibers were much swollen and had compressed the surrounding tissue slightly. This swelling seems to have been due to myxomatous degeneration, which was marked, especially in the more central portions of the

tumor. The length and the thickness of the fibrils varied markedly. Many small fine fibrils could be seen between parallel coarse fibrils (fig. 1). With van Gieson's stain there was considerable variation in the tinctorial reaction, which ranged from yellow to orange to deep red. In the photomicrograph, cells in varying stages of degeneration can be seen between parallel fibers. The fibers were applied to the surface of the cell so that it appeared as though they were laid down along the surface of the cell columns in an arrangement similar to that described by Masson for experimental schwannomas. In some regions a suggestion of a palisade arrangement of nuclei can be seen.

Some long fibrils were not directly associated with nuclei, whereas others had several associated with them in linear fashion. Many of the nuclei were elongated, at times bent on themselves and frequently

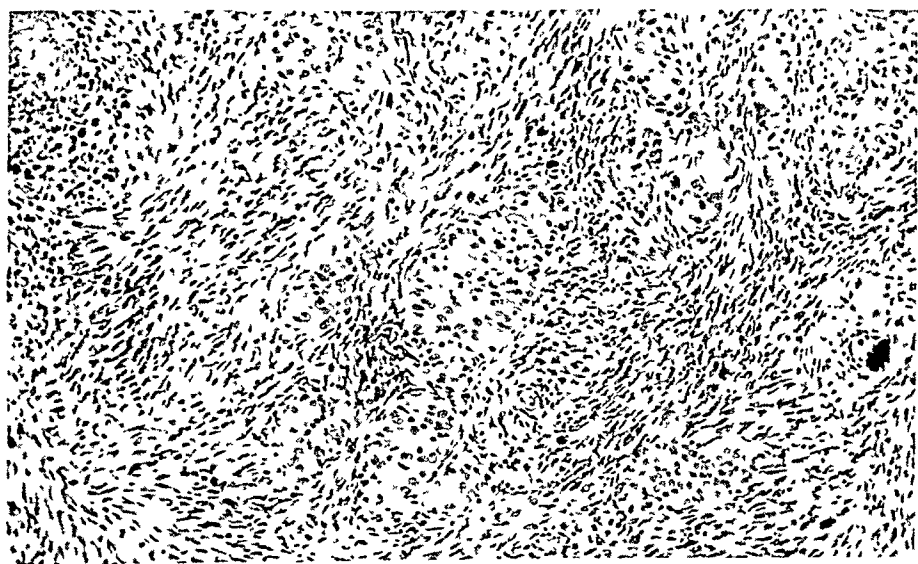


Fig. 2.—Low power magnification of a section which shows the epithelial masses, some of which are considerably elongated. The peripheral nuclei are seen to be perpendicularly arranged. The stroma is composed of cells with elongated nuclei showing a slight tendency toward palisade arrangement. Hematoxylin and eosin.

fissured and irregular in contour. Nucleoli were prominent in a large number of these cells. The number of nuclei varied considerably in different regions. In more cellular areas many nuclei were hyperchromatic, and mitotic figures were present in moderate numbers. The cells varied much in size and shape. Not infrequently nucleated cytoplasmic masses were connected by cytoplasmic processes, which suggested a syncytial character of some portions of the tumor. With such a structure it is possible that many of the rather broad and also of the fine fibrils were derived from these cytoplasmic masses. About some of the blood vessels the arrangement of the fibrils was similar to that in reticulated areas in other tumors of peripheral nerves.

A most interesting histologic feature of the tumor was the presence of fairly uniformly distributed round, oval and elongated epithelial-like masses (fig. 2). Some of these were solid masses composed of cells that simulated pavement cells; others had cuboidal and flattened cells arranged about a lumen. In some instances long, narrow, solid cords of epithelial cells were seen which must have been longitudinal segments of the tubular structures. The nuclei in some of these solid masses were perpendicularly arranged (fig. 2) and were interesting in comparison with a similar feature in the embryonic Schwann membrane (Nageotte⁴). The tubular arrangement may be similar to the behavior of the Schwann cells in developing and regenerating nerves, as pointed out by Masson. The histologic appearance of many of these cells was similar to that of some scattered through the stroma. This applies in particular to the nuclei. Degenerative changes were marked in many. There appeared to be a transition of some of these epithelial masses into the surrounding stroma, strongly suggesting that the epithelial-like cells, in part at least, made up the stroma. In such areas there was an increase in cellularity, in hyperchromatism and in mitoses. The nuclei of many of the cells in such areas were very irregular, frequently being lobulated as though they were undergoing amitotic division. Giant cells were seen in these areas. Keratinization could not be demonstrated in any of the epithelial-like masses.

Blood vessels were moderately numerous. Their walls varied in thickness from those apparently consisting of only an endothelial layer to others that were rather thick and hyalinized. A few vessels were partially or completely occluded by thrombi composed mainly of fibrin and red cells, but in several regions a moderate number of polymorphonuclear cells were seen in the thrombus and the surrounding area. Small hemorrhages were found scattered throughout the tumor. Changes in the vessels similar to these are seen in some of the central gliomas.

The metastases in the lymph glands (fig. 3) were composed entirely of cells similar to the epithelial-like cells in the tumor in the thigh. The cells were large; their borders were frequently indistinct, and in many of them the cytoplasm was vacuolated. The nuclei were large, irregular and frequently lobulated or fissured, with prominent nucleoli. Small areas with a myxomatous appearance similar to the stroma of the main tumor were seen in several of the nodules in the lung, demonstrating that the epithelial-like metastases had undergone changes similar to those in the primary tumor. The metastases in the lungs also contained only the epithelial-like cells. Extensive central necrosis had occurred in the largest nodes.

The prostate was carefully examined but revealed no evidence of malignant change in the epithelium. In adenomatous areas many of the acini were considerably dilated and contained corpora amylacea. In

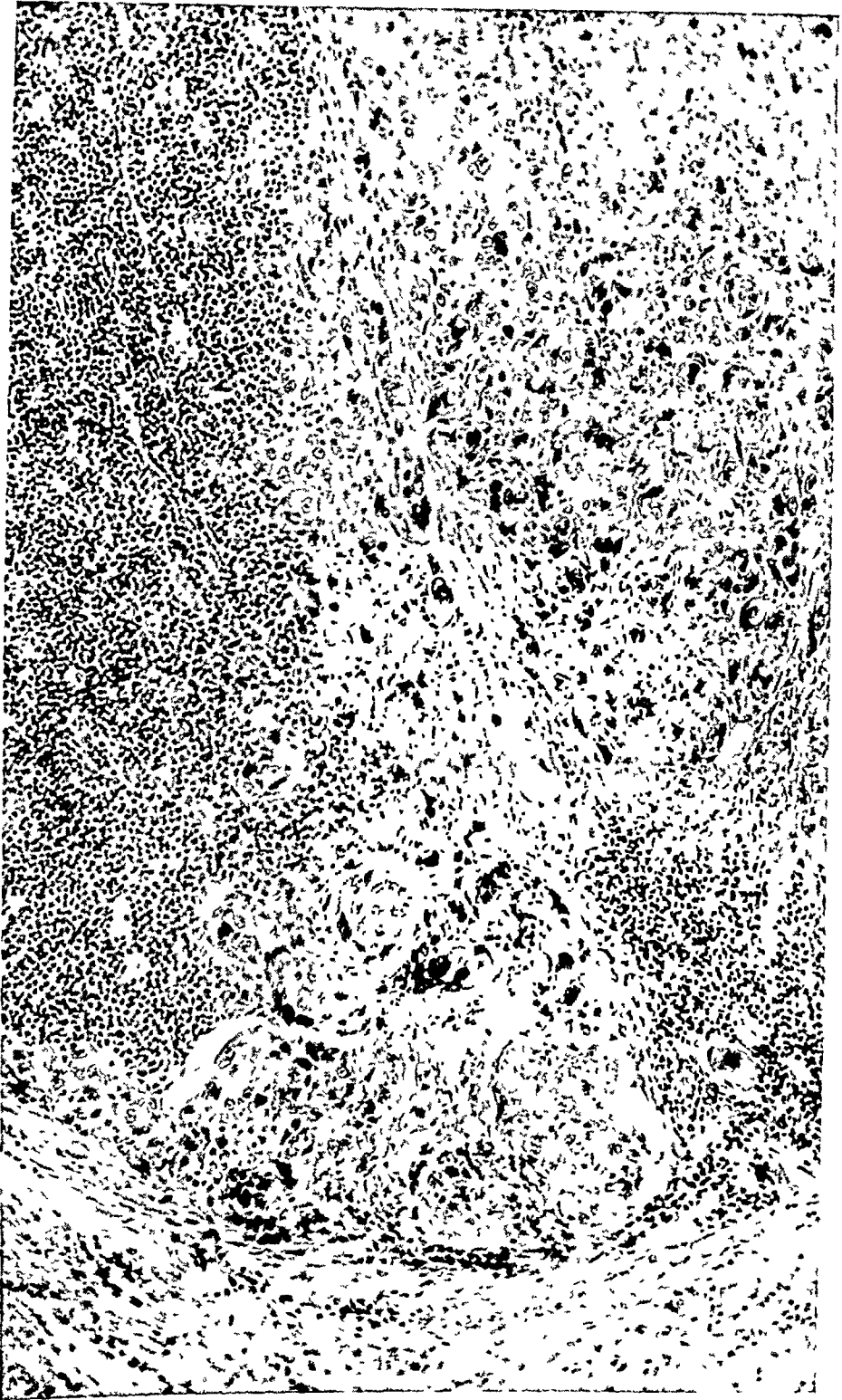


Fig. 3.—Metastatic nodules in a regional lymph node are composed of cells similar to those in the epithelial masses in the primary tumor. Hematoxylin and eosin.

several blood vessels small masses of tumor cells similar to those in the tumor of the thigh were seen. These cells were, however, entirely within the blood vessels. The examination of the prostate definitely ruled out this organ as the seat of a primary malignant growth. The epithelium was regular in its relationship to the stroma, and the cells were uniform. The tumor in the thigh was not one of a type that could be secondary to a primary carcinoma of the prostate. The epithelium, and particularly the stroma, were very different from those of prostatic carcinoma. The unilateral involvement of the pelvic lymph nodes is more in favor of a primary tumor in the thigh.

A primary carcinoma of the lung could produce metastases in a neurogenic sarcoma of the thigh. The bilateral peripheral involvement of the lungs by innumerable small nodules in the peripheral portion of all lobes is against such an interpretation. The bronchi were free from involvement, as were also the mediastinal lymph nodes. The metastatic involvement of the left iliac lymph nodes was of longer duration than that in the lungs because of the greater amount of necrosis, and also the greater proliferation of connective tissue about some of the nodules. It would be unusual for a primary tumor of the lung to select a neurogenic sarcoma in the thigh as a favorite and almost the only site of metastasis.

A teratoma in the thigh might possibly give rise to the lesions found in this case. In such a tumor, however, the small, scattered epithelial masses that were seen throughout the mass would be unusual. If the primary growth were a teratoma one would be forced to admit that both the epithelium and the stroma were malignant, the latter most highly so, but that only the epithelial element had metastasized, which would be unlikely. Other types of tissue are commonly found in teratomas but were absent in this tumor.

Tumors arising from synovial membranes may contain epithelial-like areas. Such tumors have been reported by Smith.⁷ The structural arrangement and the appearance of the cells and of the fibrils differ from those of the tumor reported here. There was no connection with a synovial membrane of either the knee or the hip in this case. The changes in the vessels and the presence of numerous vascular spaces might suggest an endothelial origin. These changes were not as marked, however, as in other tumors not of endothelial origin, and the cells did not simulate those seen in endothelial tumors. In a sarcoma arising from muscles, fascia or osseous epithelial elements like those present in this tumor are not found.

The general features of the tumor strongly suggest a neurogenic origin. It was encapsulated and irregularly lobular and ovoid and had

7. Smith, L. W.: *Am. J. Path.* **3**:355, 1927.

undergone myxomatous degeneration to a marked degree. The arrangement in bundles of fibrils and nuclei, with some tendency toward a palisade arrangement of nuclei, and the reticulated areas are seen in neurogenic tumors. These features are naturally not as evident in a neurogenic sarcoma. The presence of the epithelial-like elements can be explained as masses of Schwann's cells which may assume epithelial-like characteristics because the sheath of Schwann is derived from the embryonic ectoderm. Epithelial elements have been found in nerves and in tumors derived from nerves by others, and have been explained on that basis. Many histologic features in this case fit in with descriptions of experimental schwannomas given by Masson and Nageotte. Tumors of this type strongly suggest that they are derived from the sheath of Schwann and that this sheath can give rise to collagenous-like fibers. In interstitial hypertrophic neuritis of Dejerine and Sotta there is a progressive increase in interstitial tissue which some authors consider as due to a proliferation of the Schwann cells.⁸ The neurogenic sarcomas as a rule do not metastasize to the lymph nodes, and metastases occur late, but in a tumor in which along with rapid growth there is marked degeneration, cells may be liberated into the blood and the lymph spaces more readily. Cells with long processes could not be so readily freed from their locations.

CONCLUSIONS

A solitary tumor occurring in the thigh with many features similar to schwannomas described by other authors is reported.

The clinical features of note were severe pain in the thigh of five months' duration and the rapid increase in size of the tumor.

Histologic study indicated that the epithelial-like structures were the most important elements of the tumor and that they, in part at least, if not entirely, gave rise to the stroma.

The rapid growth and the associated degeneration were probably important in the production of metastases.

It was considered worth while to report this case because the growth represents an early stage of development of this type of tumor.

8. Wolf, A.; Rubinowitz, A. H., and Burchell, S. C.: *Bull. Neurol. Inst. New York* 2:373, 1932.

COMPENSATORY HYPERTROPHY OF THE THYROID GLAND IN GUINEA-PIGS

EFFECT OF POTASSIUM IODIDE AND OF ANTERIOR LOBE PITUITARY EXTRACT

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ST. LOUIS

In the present investigations I have carried out two series of experiments. In the first the experiments of Loeb, who had shown that the feeding of potassium iodide in small doses to guinea-pigs on the average increased compensatory hypertrophy of the thyroid gland, were repeated. It was desired particularly to determine whether if after the administration of such doses compensatory hypertrophy occurred it was accompanied by an increased number of mitoses, a question which previous investigations had not decided. In the second series the effect of anterior lobe pituitary on compensatory hypertrophy of the thyroid gland in guinea-pigs was studied. In particular was it wished to determine whether the original size of the gland was more readily reestablished following the administration of anterior lobe pituitary. In order to effect compensatory hypertrophy of the thyroid gland, one whole lobe and two thirds or three fourths of the remaining lobe were extirpated.

EFFECT OF POTASSIUM IODIDE

In several series of investigations Loeb¹ and later Gray,² in this laboratory, showed that the feeding of potassium iodide to guinea-pigs in which a great part (from one and two-thirds to one and four-fifths lobes) of the thyroid gland has been extirpated does not prevent or even diminish the resultant hypertrophy of the gland, but that on the contrary the occurrence of hypertrophy is more frequent and thus the average degree of hypertrophy is greater than in animals which have not received potassium iodide. Doses varying between 0.1 and 0.01 Gm., especially the daily administration of 0.05 or 0.01 Gm., were effective. However, certain variable factors enter into this type of experiments; thus a loss in weight during the period following the operation was found to be unfavorable for the production of marked hypertrophy.

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1. Loeb, Leo: J. M. Research **40**:199, 1919; **41**:481, 1920; Am. J. Path. **2**:19, 1926; **5**:71 and 79, 1929.

2. Gray, S. H.: J. M. Research **5**:415, 1929.

In the present investigations these experiments were continued and extended; in particular it was desired to determine whether smaller doses of potassium iodide also had an effect on compensatory hypertrophy. Furthermore, it was desired to determine whether if after the administration of such doses compensatory hypertrophy occurred it was accompanied by an increased number of mitoses.

Two series of guinea-pigs were given, for ten and twenty days, respectively, daily oral doses of 0.1, 0.005 and 0.002 Gm. of potassium iodide in the form of pills. The feeding was begun one day after one and two-thirds lobes of the thyroid gland had been extirpated, and the animals were killed one day after the last dose had been given, the remnants of the gland being removed at that time and then sectioned serially. Mitoses were counted in four pieces of the gland in each animal in the control series as well as in each of the animals to which potassium iodide had been administered. As a rule, the mitoses were counted in five sections in each piece. This was sufficient to give an approximate estimate of the number present.

Series A.—Twenty doses of potassium iodide were administered during a period of twenty days following partial thyroidectomy.

GROUP 1 (Controls).—The greater part of the thyroid gland was extirpated, but the animals did not receive potassium iodide.

Eight guinea-pigs, weighing from 170 to 205 Gm., with an average weight of 190.6 Gm., were used. Seven animals gained on the average 16.1 per cent, while one lost 15 per cent, of the original weight. The average number of mitoses in the remaining parts of the glands was 240.

The average degree of hypertrophy of the gland in this group was very low. In four guinea-pigs the colloid remained hard; few phagocytes and few mitoses were seen, and the epithelium was of low cuboidal type. In four animals some hypertrophy was noticeable, with beginning softening of the colloid as evidenced by more considerable peripheral vacuolation and a lighter staining of this material. There were a few phagocytes, and, some, though on the whole infrequent, mitoses, except in one animal in which the epithelium was higher than in the others but was still cuboidal. In this case we found, contrary to what is usually observed, that although the animal lost weight it showed softer colloid, higher epithelium and more irregularity of the acini than the others. There were few mitoses and few phagocytes.

GROUP 2 (Dosage: 0.01 Gm.).—Seven guinea-pigs, weighing from 170 to 225 Gm., with an average weight of 198 Gm., were used. Six animals gained on the average 12.6 per cent, while one lost 2 per cent, of the original weight. The average number of mitoses was 885.

In five animals a great deal of hypertrophy was noted, most of the colloid having been absorbed; the acini were irregular; many mitoses were seen, and the epithelium was high cuboidal; the number of phagocytes was moderate except in one specimen in which many were noted. The appearance of the acini varied in the same section from those with slitlike lumens to those with widely dilated lumens containing soft colloid. In the two animals which showed very little hypertrophy the colloid remained, on the whole, hard with some beginning softening; there were few phagocytes and mitoses, and the epithelium was low cuboidal, although a little higher than in the normal guinea-pigs. The acini were regular in these two animals.

GROUP 3 (Dosage: 0.005 Gm.).—Seven guinea-pigs, weighing from 175 to 225 Gm., with an average weight of 195 Gm., were used. Two lost 3.5 per cent of their original weight; five gained an average of 11 per cent. The average number of mitoses was 585.

In four animals there was a great deal of hypertrophy, with soft colloid, high to medium cuboidal epithelium and irregular acini. The number of phagocytes was not great. In three animals there was only a moderate degree of hypertrophy, much of the colloid being relatively hard, with only beginning softening and vacuolation. The epithelium varied in height from low to medium cuboidal in these three, and the acini remained regular.

GROUP 4 (Dosage: 0.002 Gm.).—Six guinea-pigs, weighing from 185 to 225 Gm., with an average weight of 202 Gm., were used. One lost 5 per cent of its original weight, and five gained 24 per cent. The average number of mitoses was 720.

Five of the animals showed about the same degree of hypertrophy as the animals which received 0.005 Gm. Most of the colloid had been absorbed, and that which remained appeared as pale pink wisps; the epithelium varied from medium to high cuboidal, and the acini were irregular. As was found elsewhere also, in the same piece of the gland and in the same section the colloid sometimes varied from hard to soft, but on the whole there was relatively little hard colloid. There were many mitoses and a number of phagocytes. The acini were not as irregular as those in the animals which received the larger doses. In the one animal which showed only about the same degree of hypertrophy as that found in the controls, the colloid was hard, and few phagocytes and mitoses, low cuboidal epithelium and regular acini were noted.

Summary.—The number of guinea-pigs showing evidence of compensatory hypertrophy of the thyroid gland and the degree of hypertrophy were greater in the groups fed potassium iodide than in the control group. There was more hypertrophy in the animals which received doses of 0.01 Gm. than in those which received smaller doses. However, there was not much difference in the degree of hypertrophy between the animals which received 0.005 Gm. and those which received 0.002 Gm. The number of phagocytes was not prominent, probably because the quantity of iodine administered was in general small. However, in several instances, many phagocytes were observed after the administration of the larger doses. In general, the number of mitoses approximately paralleled the degree of hypertrophy. There is a variegation in the structure after the administration of potassium iodide, for in the same section may be found acini lined with low cuboidal epithelium filled with hard colloid, alternating with acini from which the colloid has been absorbed, resulting in their collapse. This variegation in structure was observed by Loeb³ in the study of intact thyroid glands in guinea-pigs treated with potassium iodide.

Series B.—Ten doses of potassium iodide were administered during a period of ten days following partial thyroidectomy.

GROUP 1 (Controls).—The greater part of the thyroid gland was removed, but no potassium iodide was administered.

Five guinea-pigs, weighing from 190 to 230 Gm., with an average weight of 206 Gm., were used. The average gain in weight was 7 per cent; three animals

3. Loeb, Leo.: *Endocrinology* **13**:49, 1929.

gained, and the weight of the other two remained stationary. The average number of mitoses was 175.

In one animal there was considerable hypertrophy. Most of the colloid had been absorbed. Many phagocytes and many mitoses were observed; the epithelium was high cuboidal; the acini were irregular in shape, and many of their lumens were reduced to slits. In the other four guinea-pigs the remnants of the gland showed little hypertrophy. The colloid was hard; there was some peripheral vacuolation in the colloid which took a lighter stain with eosin; the number of mitoses was very small, and the phagocytes were infrequent except in one piece; the epithelium was cuboidal, and the acini were regular. It is of interest to note that the two animals which showed the most marked hypertrophy were the ones which gained the most in weight.

GROUP 2 (Dosage: 0.01 Gm.).—Four guinea-pigs, weighing from 200 to 235 Gm., with an average weight of 209 Gm., were used. One of these animals lost 22.5 per cent of its original weight; the others showed an average gain of 14 per cent. The average number of mitoses was 555.

There was only a moderate amount of hypertrophy. In two animals the consistency of the colloid ranged between hard and slightly soft; there was some peripheral vacuolation; many phagocytes and mitoses were present, and the epithelium varied in height from medium to high cuboidal. The other two animals showed little if any hypertrophy; the colloid remained hard; very few phagocytes and mitoses were present, and the epithelium was of the low cuboidal type.

GROUP 3 (Dosage: 0.005 Gm.).—Six guinea-pigs, weighing from 195 to 250 Gm., with an average weight of 210 Gm., were used. Five of these on the average gained 11 per cent, while one lost 8 per cent, of the original weight. The average number of mitoses was 300.

In four animals there was moderate hypertrophy with variation of the colloid from hard to soft. In one of these, there were many phagocytes and many mitoses and the epithelium varied from low to high cuboidal. The rest did not show many phagocytes or many mitoses, and the epithelium was from low to medium cuboidal. The animal which showed the greatest hypertrophy gained the most in weight. Two animals showed only a little hypertrophy. The colloid was hard; few phagocytes and mitoses were observed, and the epithelium was low cuboidal. One of these animals had lost in weight.

GROUP 4 (Dosage: 0.002 Gm.).—Four guinea-pigs, weighing from 210 to 240 Gm., with an average weight of 223 Gm., were used. Three gained on the average 2 per cent, while one lost 2 per cent, of the original weight. The average number of mitoses was 30.

There was little hypertrophy in this group, even less than in the control animals. In three animals the colloid remained hard, and the epithelium varied from low to medium cuboidal. In one the colloid was beginning to soften, but the other structural characteristics remained the same as in the other three. The acini were regular, and there were few phagocytes except in the animal in which the colloid was beginning to soften.

Summary.—In this series there was a moderate amount of hypertrophy of the thyroid gland in the animals which received 0.01 and 0.005 Gm. of potassium iodide. The degree of hypertrophy was higher in these animals than in those which received 0.002 Gm., and it was also higher than in the controls. However, the controls showed at least

as much hypertrophy as, and in some cases even more than, did the animals which received the lowest dose.

CONCLUSIONS BASED ON EXPERIMENTS WITH POTASSIUM IODIDE

These experiments confirm the conclusion that potassium iodide increases the degree of compensatory hypertrophy which normally takes place only to a moderate degree when a great part of the thyroid gland has been removed. In addition, it was found that smaller doses than those used in the earlier experiments increase the degree of hypertrophy. Moreover, the intensity of mitotic activity is increased under the influence of potassium iodide, and in general the number of mitoses corresponds to the degree of hypertrophy.

EFFECT OF ANTERIOR LOBE PITUITARY

It has been shown in this laboratory⁴ that the feeding of tablets of anterior lobe pituitary prevents compensatory hypertrophy of the thyroid gland of the guinea-pig. On the other hand, Loeb and Bassett⁵ found that intraperitoneal injections of either acid or alkaline, subsequently neutralized solution of anterior lobe pituitary extract in daily doses of 1 cc. or even less produce changes in the thyroid gland resembling those found in intense compensatory hypertrophy. The hypertrophy may be noticeable after a single injection (Silberberg⁶), and it increases with the number of injections given until the sixth or seventh day, when an approximate maximum is reached. At the end of the second, third or fourth day, mitotic proliferation is at its height. After this period, the number of mitoses may begin to decrease, while the solution of the colloid and the hypertrophy of the acinus cells still progress. These findings suggested the problem as to the influence of the administration of anterior lobe pituitary on compensatory hypertrophy of the thyroid gland in the guinea-pig following extirpation of the greater part of this organ. In particular was it desired to determine whether as a result of these injections the normal size of the gland would be regained more rapidly.

Three series of experiments were carried out. In the first series (A), the animals were divided into three groups. In one group, one and two-thirds lobes of the thyroid gland were extirpated and 19 cc. of solution of anterior lobe pituitary was given in daily intraperitoneal injections of 1 cc., beginning the day after the operation; the animals were killed on the day following the last injection. Another group received the same doses but the thyroid was left intact. In a third group the same amount of the gland was removed but no solution of

4. Loeb, Leo.: *J. M. Research* **41**:481, 1920. Loeb, Leo, and Kaplan, E. E.: *ibid.* **44**:557, 1924. Loeb, Leo.: *Am. J. Path.* **5**:71, 1929.

5. Loeb, Leo, and Bassett, R. B.: *Proc. Soc. Exper. Biol. & Med.* **26**:860, 1929; **27**:490, 1930.

6. Silberberg, M.: *Proc. Soc. Exper. Biol. & Med.* **27**:166, 1929.

anterior lobe pituitary was injected. In the second series (B), the animals were likewise divided into three groups, but they received only ten doses of anterior lobe pituitary, beginning directly after operation. The thyroid glands were examined on the eleventh day following operation. In the third series (C), the guinea-pigs in which the greater part of the thyroid gland had been extirpated received seven doses of anterior lobe pituitary beginning fourteen days following operation. The controls, with intact thyroid glands, were also given injections during the same period.

Series A.—GROUP 1 (Controls).—Partial thyroidectomy was performed, but solution of anterior lobe pituitary was not injected. Nine guinea-pigs ranging in weight from 175 to 200 Gm., with an average weight of 189 Gm., were used. All of the animals gained weight, the average gain being 30 per cent.

There was only moderate hypertrophy. However, six guinea-pigs showed more evidence of hypertrophy than did the other three. In these six animals, the acini were filled with colloid which was beginning to soften, although it varied from hard to soft. There were infrequent phagocytes and mitoses. The epithelium was a little higher than usual, and the acini were regular in all the animals except one. In the other three guinea-pigs the colloid was still hard; there were few phagocytes, and the epithelium was, on the average, low cuboidal.

GROUP 2.—One cubic centimeter of solution of anterior lobe pituitary was given daily for nineteen consecutive days following operation. Nine guinea-pigs, ranging in weight from 172 to 200 Gm., with an average weight of 191 Gm., were used. One animal lost 2 per cent of its original weight; the others showed an average gain of 1 per cent.

In all the animals but one, a high degree of hypertrophy was observed. The acini were very irregular, with slitlike lumens, papillae and spurs; the colloid varied from hard to very soft in six of these animals. In the two guinea-pigs which showed the greatest hypertrophy little colloid was left; the epithelium was high columnar, the acini were very irregular, and there were many mitoses. Not many phagocytes were noted in these two animals. In six other guinea-pigs, which showed a little less hypertrophy, there were some mitoses, but the number was apparently not great. One animal showed only moderate hypertrophy, with relatively hard colloid, few phagocytes and mitoses, cuboidal epithelium which was somewhat higher than normal and large distended acini. This animal gained more weight than did any of the others.

GROUP 3.—Nineteen injections of solution of anterior lobe pituitary were given, but the thyroid gland was left intact. Nine guinea-pigs, ranging in weight from 177 to 235 Gm., with an average weight of 201 Gm., were used. Two animals gained and seven lost weight; the loss in weight was, on the average, 4 per cent.

All these guinea-pigs showed striking hypertrophy. In all but two by far the greater part of the colloid had been absorbed and only a few pale shreds remained; the epithelium was high columnar, the acini were irregular and showed papillae and spurs, and the lumens were often reduced to slits. In two animals, similar changes were noted but a good deal of colloid was left. In one of the two, phagocytes were frequent. Many mitoses were observed in all the guinea-pigs except the last two mentioned.

Summary.—Hypertrophy of the thyroid gland of the guinea-pig was produced in the intact gland as well as in the remnants of the partially extirpated gland as a result of the administration of anterior lobe pituitary. On the whole, the degree of hypertrophy in the parts of the

glands remaining after operation not only was no greater than that observed in the intact glands, but was somewhat less. This result may perhaps be explained by the fact that in the peripheral acini of the thyroid gland hypertrophy is always less marked than in the central parts. If a great part of the gland is extirpated and only a small remnant is left, the circumference of the small piece is relatively more preponderant than it is in the intact gland. Thus the hypertrophy may be diminished in a relatively greater number of acini as a result of the partial extirpation.

Furthermore, it was found that it is not possible by means of injections of solution of anterior lobe pituitary to accelerate the restitution of the remnant to the normal size. There was no appreciable difference in size between the remnants of the thyroid glands in the guinea-pigs which had received the extract following operation and in those which had not. If, then, one finds as a result of the injection of solution of anterior lobe pituitary, a marked increase in the size of the cells and in the number of mitoses as compared with those of the control animals, it must be due to the fact that the hypertrophy and hyperplasia produced by anterior lobe pituitary change the structure of the remaining portion of the gland without an actual expansive growth becoming manifest. One must assume that the spaces where formerly colloid was present are occupied by cellular elements.

Series B.—GROUP 1 (Controls).—Partial thyroidectomy was performed, but the animals did not receive anterior lobe pituitary. Seven guinea-pigs, ranging in weight from 195 to 240 Gm., with an average weight of 216 Gm., were used. One animal lost 2 per cent of its original weight; the remaining six gained, on the average, 11 per cent.

In three animals there was moderate hypertrophy, with softening and vacuolation of the colloid, slightly enlarged epithelium and regularly shaped acini. Many phagocytes appeared in one of the animals, which showed the greatest softening of the colloid. Some mitoses were noted in each animal, and they were frequent in one. Four animals showed only slight hypertrophy, with hard colloid, few phagocytes and mitoses, only slightly enlarged epithelium and regular acini.

GROUP 2.—One cubic centimeter of solution of anterior lobe pituitary was given daily for ten consecutive days following operation. Seven guinea-pigs, ranging in weight from 210 to 265 Gm., with an average weight of 225 Gm., were used. Three animals gained and four lost weight, the average loss being 2 per cent.

Three animals showed a great deal of hypertrophy, with high cuboidal epithelium, irregular acini with slits and spurs and greatly softened colloid. The other four showed a little less hypertrophy, with more regular acini, medium cuboidal epithelium and more remaining colloid. The number of phagocytes and mitoses was not striking in any of the animals.

GROUP 3.—Ten cubic centimeters of solution of anterior lobe pituitary was given, but the thyroid gland was left intact. Seven guinea-pigs, ranging in weight from 190 to 210 Gm., were used. One of these animals gained 8 per cent of its original weight, while six lost, on the average, 6 per cent.

All the animals showed a high degree of hypertrophy. The acini were irregular, and many slits and papillae were visible; the epithelium was columnar, and the colloid had been almost entirely absorbed in all but two animals. In these two the epithelium was cuboidal, although higher than in the acini of normal guinea-pigs, the acini were fairly regular and the colloid was soft. In the guinea-pig which showed the greatest hypertrophy there were many phagocytes and many mitoses. In the others there were some phagocytes and mitoses, but their number was not great.

Summary.—The degree of hypertrophy in this series was not as high as in the preceding one, but, as in the former series, the animals which received anterior lobe pituitary without operation showed a greater degree of hypertrophy of the thyroid gland and lost more weight than the animals which received the extract after operation. The control animals, which did not receive anterior lobe pituitary after operation, showed the least hypertrophy. It should be noted, however, that this series of experiments was carried out during April and May, while the other two series were carried out during the colder months of the year. This difference may possibly account for the fact that less hypertrophy was noted.

Series C.—Seven cubic centimeters of solution of anterior lobe pituitary was given, beginning fourteen days after operation. The animals were killed on the day following the last injection. In the first group, which received 7 cc. of solution, the thyroid gland was left intact; in the second group, a great part of the gland was removed, but no injections were given, and in the third group the injections were given after a great part of the gland had been removed.

GROUP 1 (Controls).—The thyroid gland was partially extirpated, but the animals received no anterior lobe pituitary. Ten guinea-pigs, ranging in weight from 245 to 290 Gm., with an average weight of 263 Gm., were used. All of the animals gained in weight, the average gain being 32 per cent.

Nine guinea-pigs showed very slight hypertrophy of the acinar epithelium with regular acini; the colloid showed a little softening in all but two, in which it remained hard. In one animal there was more hypertrophy; a great part of the colloid had been absorbed; the epithelium was higher, and the acini were irregular, the lumens of many being reduced to slits. As a rule phagocytes as well as mitoses were not frequent.

GROUP 2.—Seven cubic centimeters of solution of anterior lobe pituitary was given following partial thyroidectomy. Nine guinea-pigs, ranging in weight from 250 to 300 Gm., with an average weight of 266 Gm., were used. All of the animals gained weight, the average gain being 26 per cent.

Seven guinea-pigs showed a high degree of hypertrophy. The epithelium was columnar, and the acini were very irregular with many slitlike lumens and papillary projections. Most of the colloid had been absorbed, and there was a moderate number of mitoses. There were some phagocytes in all these animals. Two animals showed moderate hypertrophy, with medium cuboidal epithelium; the colloid was for the most part soft, but some hard colloid was left and the irregularity of the acini was less marked. However, in one of these two animals many phagocytes and mitoses were found.

GROUP 3.—Seven cubic centimeters of solution of anterior lobe pituitary was given to animals in which the thyroid gland was intact. Four guinea-pigs, ranging in weight from 275 to 305 Gm., with an average weight of 263 Gm., were used. All of the animals lost weight, the average loss being 9 per cent.

The degree of hypertrophy in three animals was about the same as in the second group of this series, but the acini were not so irregular. The epithelium was columnar, and the colloid either had been absorbed entirely or was softened. In one animal the acini were regular and some hard colloid was left, but the epithelium was high and there were many mitoses.

Summary.—In this series the degree of hypertrophy in the thyroidectomized animals which received anterior lobe pituitary was very high and corresponded in intensity to that observed in the animals which received the extract but were not operated on. As had been noted in the preceding series, the hypertrophy was much greater in the guinea-pigs which had received anterior lobe pituitary than in those in which a part of the gland had been extirpated but which did not receive the extract. On the whole, the partially thyroidectomized animals in this series showed much greater compensatory hypertrophy than did those in the preceding series, which were given 10 cc. of solution of anterior lobe pituitary. This difference may perhaps be due to the fact that the experiment in which 10 cc. was administered was carried out during the warmer season; this interpretation agrees with previous findings of Loeb concerning the seasonal variations in the intensity of compensatory hypertrophy. However, the fact that in this series the injections were begun only fourteen days following the operation, while in the preceding series they were started directly following the operation, must also be considered. The size of the remnants of the thyroid glands was about the same in the animals which did and in those which did not receive anterior lobe pituitary. The increase in hypertrophy, therefore, does not necessarily lead to a noticeable increase in the volume of the remnant, but leads in the main to an increase in the parenchyma at the expense of the colloid, which is largely absorbed or liquefied.

GENERAL CONCLUSIONS

The hypertrophy of the thyroid gland caused in guinea-pigs by the injection of sufficient quantities of solution of anterior lobe pituitary is, on the average, much greater than the hypertrophy caused in the remaining portions of the gland by the removal of one whole lobe and the greater part of the second lobe.

While each of the two processes studied, namely partial thyroidectomy and the injection of anterior lobe pituitary, tends to cause hypertrophy of the thyroid gland, their combination does not lead to a summation of the separate effects. On the contrary, in some cases, after removal of the greater portion of the thyroid gland the hypertro-

phy of the remaining part caused by the injection of anterior lobe pituitary may be less than the hypertrophy elicited in an intact thyroid gland.

If one compares the effect of potassium iodide with that of anterior lobe pituitary on compensatory hypertrophy following extirpation of the greater part of the thyroid gland in guinea-pigs one finds that these two substances behave differently: While potassium iodide distinctly intensifies compensatory hypertrophy following partial extirpation of the thyroid gland, no summation of hypertrophic effects is produced by the administration of anterior lobe pituitary and partial thyroidectomy; on the contrary, under certain conditions there may be a diminution of the hypertrophy caused by anterior lobe pituitary as a result of previous extirpation of the greater part of the gland.

PEROXIDASE ACTIVITY OF HEMATIN

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It has long been known that blood will catalyze the decomposition of hydrogen dioxide. When benzidine, guaiac and other aromatic chromogens are present these are oxidized to blue-colored compounds. This is known as peroxidase activity. The benzidine test for blood is a practical application of the principle involved.

The present report is an outgrowth of a study of the immunologic reactions of hemoglobin and particularly globin, the protein part of the hemoglobin molecule, and the rôle that it plays in these reactions. Hektoen and Schulhof¹ found that when oxyhemoglobin was changed to methemoglobin, sulphemoglobin or carbon monoxide hemoglobin² the antigenic titer remained the same as the original compound. In my experience, too, oxyhemoglobin antiserum reacts with methemoglobin in the same dilution as oxyhemoglobin, the original antigen. Moreover, hematin itself does not form precipitins with hemoglobin antiserum. There is little doubt, therefore, that the antigenic properties of hemoglobin reside in the globin part of the molecule.

It is a well known fact that when hemoglobin is treated with acid it splits into globin and acid hematin. The separation of acid hematin from globin is difficult, and unless conditions of temperature and acidity are closely controlled the product formed is so completely denatured (insoluble in neutral solvents) that it is rendered useless for immunologic studies. According to the literature,³ the preparation of native or undenatured globin from hemoglobin is an accomplished fact. Despite this, I have been unable to prepare such a protein free from hemoglobin or hemoglobin-reacting substances. In an attempt to use the titer of an antiserum for hemoglobin as a criterion for the purity of globin preparations, the theoretical question arose: Is it not possible, when hemo-

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1. Hektoen, L., and Schulhof, K.: *J. Infect. Dis.* **41**: 476, 1927.

2. Boor, A. K., and Hektoen, L.: *J. Infect. Dis.* **46**: 1, 1930.

3. A review of the literature on globin up to 1930 is given by Anson, M. L., and Mirsky, A. E.: *J. Gen. Physiol.* **13**: 469, 1930. Later publications are those of Hamsik, A.: *Ztschr. f. physiol. Chem.* **187**: 229, 1930; Troensegaard, N.: *ibid.* **199**: 129, 1931; Schenck, E. G.: *Arch. f. exper. Path. u. Pharmacol.* **150**: 160, 1930.

globin is used as an antigen, that some of it is split in vivo with the consequent production of two precipitins; one, for the hemoglobin molecule as a unit, the other, for globin alone? If this is true the hemoglobin antiserum will give no information as to the purity of the globin preparation in question. All globin preparations reacted in low dilutions, 1 part in 1,200 to 1 part in 2,000, with hemoglobin antisera.

With regard to the problem at hand, it was also noted that these globin preparations showed distinct peroxidase activity; hence it became rather pertinent to inquire into the chemical basis for the benzidine test for blood.

In preliminary tests it was observed that hematin shows a strong peroxidase activity. To obtain a quantitative estimate of this activity as compared with whole blood, it was necessary to prepare pure hematin. Nencke and Zaleski⁴ have described a satisfactory method for the preparation of acid hematin. Elvehjem's⁵ modification of the older methods was the one used in this study.

METHOD

If the whole blood is added drop by drop to a 95 per cent solution of hot acetic acid containing a trace of sodium chloride, crystalline hematin hydrochloride is formed on cooling. The crystals are readily separated from the mother liquor by filtration or by centrifugation, washed with cold dilute acid and alcohol, and dried. To insure absolute purity, the first product was recrystallized according to the method of Schälfejeff as described by Nencke and Zaleski.⁴ Equal quantities of hemin and quinine (base) were dissolved in warm chloroform, and this solution was slowly added to hot acetic acid. As in the original preparation, constant stirring and the presence of sodium chloride are necessary. The crystals thus obtained gave on analysis for iron, figures which agreed with the formula $C_{34}H_{38}O_4N_4FeCl$ for hemin. The theoretical figure for iron was 8.59 per cent; the average of analyses, 8.54 per cent. The crystalline form and appearance of hemin did not change on recrystallization.

A known weight of recrystallized hemin was dissolved in dilute sodium carbonate, and successive dilutions of 1 part in 10, 1 part in 100, etc., were made. At the same time, samples of fresh blood were obtained and hemoglobin determined on the basis of iron. Knowing the iron content of hemin and that of the samples of blood, the peroxidase activity of each was compared at successive dilutions on the basis of the same iron content. This was carried out in a porcelain spot plate, 1 drop of benzidine in glacial acetic acid, 1 drop of the solution to be tested and 1 drop of 3 per cent solution of hydrogen dioxide being used. In every trial it was observed that the peroxidase activity of hematin was equal to that of blood. In dilutions of 1 part in 100,000, the hematin solution gave distinctly more positive reactions. The limit of the reaction is about 1 part in 200,000 or slightly higher.

These observations with respect to the chemical basis for the blood-benzidine reaction are by no means original with me. After making

4. Nencke and Zaleski: *Ztschr. f. physiol. Chem.* **30**:384, 1900.

5. Elvehjem, C. A.: *J. Biol. Chem.* **93**:203, 1931.

preliminary tests, it was found that Wu,⁶ in 1922, not only reported the peroxidase activity of hematin, but also described a quantitative method for the determination of hemoglobin by using this activity of hematin as a standard of comparison. More recently, modifications of Wu's method were reported by Bing and Baker.⁷ Improvements in the qualitative application of the test were described by Ingham.⁸ As the test is applied to acid-ether extracts of gastric contents, urine, feces and other biologic materials it is a test for hematin and not for hemoglobin. Moreover, native globin free from hemoglobin and hematin will in all probability not give the test.

CONCLUSION

It appears that hematin is responsible for the peroxidase activity of blood.

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Laboratory Methods and Technical Notes

A SIMPLIFICATION OF THE COOLED KNIFE METHOD (SCHULTZ-BRAUNS) FOR OBTAINING FROZEN SECTIONS

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In 1931, Schultz-Brauns¹ described a modification of the method for obtaining frozen sections for which he claimed certain advantages over the commonly used technic. He developed an apparatus with which the knife could be cooled below the freezing point (approximately — 5 C.). A second tubing was attached to the carbon dioxide tank and connected with a special outlet which was fixed between the holders of the knife. By the opening of a valve, carbon dioxide could be sprayed on the knife which thereby cooled to the proper temperature. Sections cut with the cooled knife were taken from the knife directly to the slide. Schultz-Brauns pointed out that even very friable tissue, such as is found not infrequently in tumors and necroses, could be cut and attached to the slide without losses or other difficulties. The contents of glands and cysts were not dislocated or lost when this method was used, while this often occurred in sections cut by the common technic. Fixed and unfixed tissues could be cut with equal ease. The stained sections compared well in quality with those prepared with the paraffin method. He found his technic, moreover, useful in the preparation of sections for ashing, because the sections cut with the cooled knife did not come into contact with any agent (fixation and dehydration fluids) which was apt to change the amount and distribution of the mineral constituents of the cells.

TECHNIC

During recent investigations which necessitated the use of frozen sections, a simple apparatus was developed which seems to work just as well as the somewhat complicated and specially constructed arrangement of Schultz-Brauns. This can be built with practically no cost or special technical skill, and it has the advantage of keeping the knife at the proper temperature for about from five to ten minutes without any attention, while the apparatus used by Schultz-Brauns requires a spraying of the knife at intervals of one minute.

A rectangular trough was constructed of thin tinned plate which could be cut with wire shears. It measured 3 by 1 by 1 inch (7.6 by 2.5 by 2.5 cm.). It was just large enough so it could be squeezed between, and be retained by, the two holders of the microtome knife. One half of the bottom of the trough was then cut out. When the trough was put into place, the open part of the bottom was so placed that it rested on the back half of the knife, while the closed portion of the

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bottom of the trough extended beyond the knife backward. The trough was then packed with carbon dioxide snow, or with "dry ice" when it was obtainable. Through the direct contact with the carbon dioxide the knife was cooled to the proper temperature. The piece of tissue to be cut was then placed on the peripheral part of the freezing platform in such a way that the knife would have to pass over almost the entire platform before hitting the tissue block. This arrangement is important for the subsequent easy removal of the section from the knife. After the tissue was properly frozen, the knife was carried through the tissue block in such a way that the section remained attached to the block with a narrow margin. The rolled up, still frozen section was flattened out on the cold knife with the help of a fine, long-haired brush. The temperature of the knife did not allow a thawing of the section. A slide was then brought into contact with the section, which became readily attached to the warm slide and stuck to it. The section was then ready for further treatment or direct examination.

It was of advantage to place sections from unfixed material (after mounting them on slides) in 95 per cent alcohol for a few seconds before putting them into hematoxylin, as thereby more clearly stained pictures were obtained and no disturbing precipitations of dye resulted. After some experience with the technic had been obtained, serial sections could be cut. The stained sections were in many respects as good as paraffin sections and were occasionally even better than these, when the tissue contained cells of rather delicate structure, such as are sometimes present in certain tumors, where the usual preparation for paraffin sections resulted in more or less marked distortions owing to excessive shrinkage.

COMMENT

The claims made by Schultz-Brauns for his method of obtaining frozen sections with the cooled knife are confirmed. The method is simple and quick, and gives much better results than those obtained with the common technic, especially when unfixed tissues are used. It is therefore particularly well suited to the preparation of quick frozen sections from biopsy. It represents the method of choice for sections to be ashed, as it is the only method which allows relatively reliable comparative qualitative and quantitative studies of the mineral content of cells. It may also be applied with advantage to the investigation of vitally stained tissues or of colored deposits and precipitations which are soluble in water or the agents used in the preparation of paraffin sections. With the simple and inexpensive apparatus described, the method of obtaining frozen sections with the cooled knife can be recommended for general use in place of the commonly used technic.

General Review

HODGKIN'S DISEASE

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(Concluded from page 562)

CHEMISTRY

The chemical aspects of Hodgkin's disease are little known. The following data are taken from isolated sources in the hope of building up this phase of the subject. Reports based on the leukemias and similar conditions are included in order to show similarities or differences. Chemical studies in this field are necessarily greatly affected by a number of variables, such as the point of localization, the special organs affected and the concurrent disease processes.

Starlinger and Winands found that in lymphogranuloma the blood shows a normal total protein content, an absolute and relative increase in fibrinogen, a moderate absolute and relative increase in globulin and a significant absolute and relative decrease in albumin. In the cachexia of lymphogranulomatosis, the protein content shows a progressive decrease, and the globulin returns to a normal value, with the relative increase preserved. Under favorable irradiation the protein content is normal; globulin shows a high normal value; albumin, a low normal value, and fibrinogen a moderate relative and absolute increase. The authors gave an extensive review of the literature.

Studies on blood cholesterol are more numerous. Currie, in a case of lymphogranuloma, found a value of 250 mg. per hundred cubic centimeters indicating a slight decrease. Freifield's case showed a content of 136 mg. Luden observed a case of Hodgkin's disease for two years, making determinations of cholesterol at weekly intervals (the condition later became generalized lymphosarcoma, according to him). After radium treatment, the pure cholesterol was decreased, and the split cholesterol increased. After roentgen treatment this proportion was reversed, pure cholesterol being increased and split cholesterol decreased. Luden remarked that when the pure cholesterol was increased, together with reduction of split cholesterol, new nodal enlargements would be found. This change always seemed to herald a recurrence. In another

paper, Luden stated that a diet which increases the blood cholesterol also causes lymphopenia, and that the same phenomenon occurs in persons predisposed to carcinoma. Sanders, working along similar lines, found that a diet leading to elevation in the blood cholesterol will produce an associated increase in polymorphonuclears with lymphopenia, and vice versa. Stenhouse, after a study of tropical hydrocele, expressed the belief that cholesterol has something to do with the production of lesions associated with obstruction of lymph channels. Generally speaking, the location of the lesion in the lymphogranulomatous process, (e. g., a close anatomic relationship to the liver or pancreas) would conceivably have considerable influence on the amount of cholesterol. Twort estimated the blood lipase, finding a decrease in lymphogranuloma and in certain diseases of the blood, which was not differential. Happold and Taylor estimated the lipase content of several organs in tuberculosis, finding a reduction in the liver and the spleen, and a value close to normal in the lungs. Twort found that in the liver the amount of lipase varied according to the amount of remaining parenchyma, and that the amount was not specific according to the disease present. Susman and Happold came to the conclusions (in connection with tuberculosis) that proliferation of the functioning cells of an organ causes an increase in its lipolytic activity, that necrosis establishes a decrease according to the extent of the lesion, and that proliferation of the stroma also causes a decrease, but less than that produced by necrosis. They stated finally that the reaction varies according to the damage to the cells and not according to the disease.

The basal metabolic rate in lymphogranulomatosis and in leukemia has been studied by Holbøll. He found the rate generally increased; when it was lowered during treatment the general condition was improved. A continued high value signified a poor prognosis. The rise is ascribed to some of the accompanying symptoms, especially the emaciation. Krantz, in 30 cases of lymphoblastoma, found that the basal metabolic rate was elevated but that it could be reduced by proper irradiation. Leukopenia is not a contraindication to irradiation in cases in which the basal metabolic rate is increased. The basal metabolic rate is valuable in the determination of therapy and of prognosis. Baldridge and Awe often found it elevated in all types of "lymphoma."

Ordway found that radium treatment of an enlarged spleen in leukemia increased the proteins, total nitrogen, urea, ammonia and phosphates of the urine. The urinary changes are due partly to products derived from autolysis of bone marrow under the influence of irradiation.

Ehrlich's diazo-reaction was reported to be positive in two thirds of cases by Borsutzky, a finding corroborated by several other writers.

Rabinowitch stated that a diazo-reaction is not found in any condition unassociated with severe renal damage. Andrewes' modification of Hewitt's test was used, and the work was done in connection with uremia. Isaacs stated that the diazo-reaction is often positive in lymphogranuloma without visible enlargement of the lymph nodes (Ziegler's larval or typhoid form).

Galloway reported the finding of Bence-Jones protein in lymphogranuloma. The relationship between this substance and renal insufficiency was discussed by Bannick and Greene, who found them frequently associated. Perhaps the appearance of this protein is the result of renal damage, and not as intimately related to involvement of the bone marrow as is usually stated. Schmidt reported an increase in the amino-acids of the blood in leukemia, especially of the myelogenous variety.

Urechia and Goia called attention to the value of examination of the spinal fluid. The colloidal gold test gave incomplete precipitation in tubes 2 and 3, as is common in tumors, but not in meningitis, in which the curve is longer and deviated to the right. This was confirmed in some cases by Mathieu, and by Thomas and Paix, who found an increase in albumin and a prolonged benzoin curve. Urechia and Goia's case showed involvement of the dura but little involvement of the pia arachnoid at autopsy, thus confirming their findings.

Vasiliu and Goia, in 3 cases of abdominal Hodgkin's disease, found that the gastric juice always showed hypo-acidity or anachlorhydria. Brack, in a case in which pruritus was present, found that a test of alimentary hemoclasia (ingestion of 200 cc. of milk) produced a marked reaction, the calcium-potassium quotient showing a definite fall. This reaction he interpreted as indicating a parasymphaticotonic disturbance.

IMMUNOLOGY

De Negri and Mieremet tried to obtain fixation of complement in 2 cases, using *Corynebacterium granulomatis-maligni* as antigen. From similar studies Olitsky found that *C. hodgekini* is a distinct diphtheroid organism, separable from *Corynebacterium xerosis* and *Corynebacterium hoffmanii*. Ayrosa made the complement-fixation test with a diphtheroid organism resembling *C. hodgekini*, obtaining a positive reaction in a case of Hodgkin's disease and negative reactions in cases of other lymphadenopathies.

Rosenthal used the Widal test to differentiate the larval or typhoid form of lymphogranuloma from typhoid and paratyphosis A and B, and cited a case. Twort, working with agglutination, precipitation and other test tube reactions, could demonstrate no specific antigens or antibodies in patients with Hodgkin's disease. He also found them to be reaction-

less to tuberculin, vaccines and specific antiserums (prepared from rabbits inoculated with lymphogranulomatous tissues and filtrates). This is contrary to Fraenkel and Much's results. He further attempted to produce specific antibodies in animals by the administration of emulsions of lymphogranulomatous, leukemic and normal lymph nodes. Some success was obtained in producing cyto-agglutinins. It is interesting to note that co-agglutinins for leukemic and normal tissue emulsions were rarely absent, and that they could be removed by adsorption, the specific agglutinins remaining. All the agglutinins were destroyed after one hour at 60 C. Attempts by Grumbach to agglutinate the bacillus which he isolated from the blood stream by culture were not successful.

MacNalty made estimations of the opsonic index, with normal findings (0.8 to 1.2). In a case of tuberculous adenitis with recurrent fever, the index was 1.37 after massage of the enlarged glands. He suggested the value of the opsonic index in differential diagnosis.

Fox and Farley attempted skin tests, using comminuted lymphogranulomatous tissue; the results were negative not only in Hodgkin's disease but in sarcoma (1 case) and in aleukemic leukemia (1 case). Hanrahan also tried skin tests.

Stewart and Doan investigated the phosphatid fraction of the lipoids of the tubercle bacillus as an antigen, and in the course of the work studied several cases of Hodgkin's disease. The serum of tuberculous patients frequently showed ability to precipitate the tuberculophosphatid in high titer. In 9 cases of Hodgkin's disease "the presence of free phosphatid-antigen was suggested in tests with antisera for avian phosphatid, four of the cases also giving a positive precipitin reaction with anti-human tuberculo-phosphatid serum." This antiserum was prepared from rabbits, and the reactions were obtained in the patients' serum. It is also to be noted that in 24 cases of verified Hodgkin's disease precipitation with human tuberculophosphatid occurred in various titers as follows: 160—all cases; 320—23 of 24; 640—20 of 24; 1280—8 of 24; 2,000—2 of 24. These results are striking, especially when compared with the results obtained in other diseases clinically and anatomically resembling Hodgkin's disease, in none of which, with the exception of 3 cases of pseudoleukemia, were such numerous positive reactions found.

CLASSIFICATIONS AND RELATIONSHIPS

Simonds, in his review, considered the relation of Hodgkin's disease to other diseases of the lymph nodes and the possibility of its sarcomatous transformation. His emphasis on the ignorance of etiologic factors in these diseases is to the point, for certainly no fully acceptable

genetic classification can be made until an advance in the knowledge of the etiology has been accomplished. He logically suggested the adoption of Ewing's view that clear histologic distinctions be maintained between the various forms of enlargement of the lymph nodes, in order not to retard the discovery of etiologic factors. Because of the uncertain state in which this matter of relationships and classification of diseases affecting lymph nodes and the hematopoietic system is found, this review will be limited to a presentation of the following outstanding classifications, with supplementary citations from the literature on general relationships.

Baldrige and Awe—

Lymphoma

1. Sclerosing type (Hodgkin's disease)
2. Endothelial type (lympho-epithelioma)
3. Lymphoblastic type (lymphosarcoma)
4. Lymphocytic type
 - (a) With leukemia (lymphatic or lymphocytic leukemia)
 - (b) Without leukemia (pseudoleukemia or aleukemic leukemia)

Klein—

Lymphoblastoma (occurring in the skin)

1. Leukemia
2. Lymphosarcoma
3. Granuloma fungoides
4. Hodgkin's disease
5. Sternberg's leukosarcoma
6. Kaposi's lymphoderma perniciosa

Bunting and Yates—

I. Hodgkin's disease; terminal pictures

1. Almost complete sclerosis (typical fibroblastic proliferation)
2. Sarcomatoid picture (atypical fibroblastic proliferation)
3. Endotheliomatoid picture (atypical endothelial proliferation, usually with marked giant cell formation)

II. Lymphoblastic group

Large cell proliferation infiltrating the whole gland, apparently due to proliferation of the large cells of the germinal centers; may become fibrous with giant cells

III. Lymphocytic group

Diffuse proliferation of small lymphocytes with very early loss of architecture; scattered lymphoblasts and atypical endothelioid cells may occur

(Transition forms between any of these groups may occur)

Hasen—

I. Lymphomatoses

1. Leukemic (lymphatic leukemia)
2. Aleukemic (Hodgkin's disease and mycosis fungoides)

II. Myelomatoses

1. Leukemic (splenomyelogenous leukemia)
2. Aleukemic (multiple myeloma)

III. Lymphosarcomas

1. Leukemic (leukosarcoma)
 2. Aleukemic (lymphosarcoma)
- (Mixed types theoretically possible; leukemic types may have aleukemic stages, and vice versa)

Minot and Isaacs—

Lymphoblastoma (malignant lymphoma)

1. Lymphatic leukemia (lymphocytic and lymphoblastic)
2. Aleukemic lymphatic leukemia
3. Pseudoleukemia (aleukemic lymphadenosis)
4. Lymphocytoma
5. Hodgkin's disease (lymphogranuloma)
6. Lymphadenia
7. Lymphomatosis
8. Lymphosarcoma
9. Round cell sarcoma
10. Leukosarcoma
11. Lymphadenosarcoma
12. Banti's disease
13. Chloroma
14. Mikulicz's disease

Pappenheim (according to Dickinson and Lwow)—Diseases of the hematopoietic system

I. Generalized leukocytomatosis (all the leukemias)

1. Lymphadenosis.
 - (a) With leukemic blood
 - (b) Without leukemic blood
2. Myelosis
 - (a) With leukemic blood
 - (b) Without leukemic blood

II. Generalized granulomatosis, including Hodgkin's disease and all generalized inflammatory diseases of the lymph nodes, such as tuberculosis, syphilis and Banti's disease

Rieux (adding to Pappenheim's classification)—

I. Lymphadenosis

- (a) With or without leukemic blood
 1. Benign or malignant
 2. Generalized or localized

II. Myelosis

- (a) With or without leukemic blood
 1. Benign or malignant
 2. Generalized or localized

(All possible combinations may be met with; in designating the disease, the terminology just given is used; for example, lymphatic leukemia becomes "benign generalized leukemic lymphadenosis," and lymphosarcoma is called "localized malignant aleukemic lymphadenosis")

Sternberg—

Pseudoleukemia, to include

1. Lymphosarcoma
2. Lymphogranuloma

3. Plasmoma

4. Diseases with hyperplasia of lymphoid tissue without leukemic blood

Ewing—

Tumors of Lymphoid Tissue

Origin	Anatomic Type	Clinical Type
Lymphocytes	Lymphocytoma	Simple lymphoma Tuberculous lymphoma Lymphatic leukemia Pseudoleukemia Malignant lymphocytoma
Reticulum cells	Large round cell hyperplasia or neoplasia	Granuloma malignum Myeloid leukemia Hodgkin's sarcoma Large cell lymphosarcoma
Endothelial cells	Endothelial hyperplasia or neoplasia	Endothelial hyperplasia of tuberculosis, etc. Endothelioma

Ceelen and Rabinowitch—

Hematoblastoses

1. Leukemic

2. Aleukemic

(a) Hyperplastic (such as myeloma and true sarcomas)

(b) Chronic inflammatory granulation tissue (such as lymphogranuloma)

(c) Tuberculosis and syphilis

Fox and Farley—

Lymph Gland Enlargements

Character of Pathologic Change	Clinical Character	Pathologic Group	No.	Specific Varieties	Association
Hyperplasia	Benign	Lymphoma	1	Lymphoma, status lymphaticus	
			2	Lymphadenoma	
			3	Glandular fever and acute leukemia	
	Malignant	Leukemia	4	Leukemia	With 5
			5	Aleukemia or generalized lymphomatosis	With 4 or 6
		Neoplasm	6	Leukosarcoma	With 5
			7	Lymphosarcoma	With 10 and 11
			8	Reticular sarcoma	
			9	Endothelioma	
Neo-inflammation	Malignant	Lymphogranuloma	10	Cellular hyperplasia	With 7 or 8
			11	Fibrosis	With 7 or 8
Inflammatory	Benign	Adenitis	12	Simple	
			13	Purulent	
			14	Tuberculous	With 11
			15	Syphilitic	

Goormaghtigh—

Lymphoid tumors (classified for clinical practice)

1. Granuloma, specific or nonspecific

2. Inflammatory hyperplasia, localized or general

3. Benign tumors: lymphoma

4. Malignant tumors:

Type 1—lymphatic leukemia

Type 2—(a) lymphosarcoma

(b) reticulo-endothelioma or reticulo-endotheliosarcoma

Between groups 1 and 4 may be placed lymphogranuloma.

The question of a possible relationship of Hodgkin's disease to sarcoma may be conveniently stated as follows (in an affirmative sense):

1. Hodgkin's disease is a form of sarcoma, beginning and ending as such, and having its origin in one of several types of cells, according to the observer—endothelial cells, reticulum cells, reticulo-endothelial cells, myeloblasts, lymphoblasts or megakaryoblasts.

2. It exists as a specific granuloma, which in some cases may be transformed into sarcoma, and especially into lymphosarcoma (Sternberg; Mueller; Levin).

3. Lymphosarcoma and Hodgkin's disease may exist together in the same patient (Levin; Miller).

4. Many cases of "Hodgkin's sarcoma" originate in the epithelial reticulum cells of the thymus (Ewing).

5. Hodgkin's disease at times exhibits the quality of invasion, a characteristic of sarcoma (Chiari; Karsner; Yamasaki; Yates and Bunting).

6. Invasion is not entirely characteristic of malignancy, but has been observed in known granulomatous tissue (Simonds; Chiari).

7. While the differentiation of lymphosarcoma and Hodgkin's disease may be difficult in some stages, Hodgkin's disease sooner or later assumes its characteristic picture (Symmers).

8. The cells found in Hodgkin's disease, lymphosarcoma and lymphatic leukemia closely resemble those of chronic inflammatory lymph node processes, the only difference being in the presence of an increased number of immature cells with larger nucleoli. Without studies of the blood, it seems to be impossible to differentiate the nodes of lymphatic leukemia from those of atypical Hodgkin's disease or lymphosarcoma. It is probable that these three states have a common neoplastic cellular origin (MacCarty).

9. Hodgkin's disease is a granulomatous process and bears no relation to sarcoma (MacCallum).

Yamasaki, Dietrich, Gibbons, Coley, Chiari and Oliver have all expressed their belief that Hodgkin's disease is genetically related to sarcoma. Oliver offered arguments in favor of such a relationship between Hodgkin's disease, lymphosarcoma and endothelioma. Webster studied a series of 123 cases of lymphosarcoma, lymphatic leukemia, leukosarcoma and Hodgkin's disease, and concluded that while the first

three diseases may be considered as different manifestations of the same condition, Hodgkin's disease is probably a pathologic entity. Warthin was convinced of the relationship between Hodgkin's disease, the various forms of sarcomatous Hodgkin's disease, reticular sarcomas of the lymph nodes and various aleukemic and leukemic lymphoid tumors. These he strongly believed to form a distinct class of neoplasms, basing his opinion on his many years of observation of lymphoid tumors. Levin believed Mikulicz's disease to be a form of Hodgkin's disease, while Ziegler believed Mikulicz's disease to be only a granulomatous involvement of lymph nodes. Reiche reported an interesting case of this disease which presented some resemblance to lymphogranuloma, enlarged nodes, splenomegaly and leukopenia. Külbs also discussed this question.

Fox and Farley discussed the relationship between aleukemic leukemia, pseudoleukemia and malignant granuloma and pointed out the histologic and clinical differences. Herriman and Rahte cited a case of thymoma which clinically resembled Hodgkin's disease, and Helvestine called attention to the close histologic resemblance of some thymomas to Hodgkin's disease. Ewing's description of lympho-epithelioma appears to be somewhat similar to the classic picture of Hodgkin's disease. His views on Hodgkin's sarcoma and thymoma are well known. Ceresoli reported the occurrence of lymphogranuloma and lymphangio-endothelioma in the same patient, and of lymphogranuloma with Hodgkin's sarcoma and spindle cell sarcoma.

Banti recognized that splenic anemia may be accompanied by enlargement of the lymph nodes, and that the changes in the spleen in Banti's disease and pseudoleukemia splenolymphatica are similar. He thought it possible to regard Banti's disease as Hodgkin's disease of the spleen. This connection was further emphasized by Yates, Bunting and Kristjanson, on the basis that a diphtheroid organism obtained from the spleen in 2 cases of Banti's disease, when injected into animals, reproduced the lesion.

Regarding true Hodgkin's disease and Hodgkin's sarcoma, Barron held that the sarcoma is engrafted on the inflammatory tissue of Hodgkin's disease and is not to be regarded as an integral part of the disease. Symmers stated that the process begins as Hodgkin's disease but may become sarcomatous. Ewing's views are well known, especially in connection with Hodgkin's disease in the thymus.

Warfield and Kristjanson cited an unusual case in which the condition is claimed to have undergone a transition from lymphosarcoma to lymphatic leukemia and then to Hodgkin's disease. In Mueller's case 1 the condition was originally typical lymphogranuloma and later became large round cell sarcoma, many cells being present closely "resembling the giant endothelioid cells so frequently seen in Hodg-

kin's disease." In his case 2 the condition was between round cell sarcoma and Hodgkin's disease and later became typical lymphogranuloma. Yamasaki, Karsner, Welch and Levine were cited by him as reporting parallel cases. He believed that lymphogranuloma and round cell sarcoma of the lymph nodes are different expressions of the same disease process; he referred to the work of Kopsch in support of his views. Kopsch produced "a polymorphocellular sarcoma" in frogs by feeding them the larvae of *Rhabditis pellis*; he believed that the malignant changes were due to a toxin elaborated by the larvae. The sarcomas in these experiments arose from granulation tissue and might be designated as malignant granulomas.

Piney, who believed in the essential reticulo-endothelial nature of Hodgkin's disease, stated that the differences between Hodgkin's disease, lymphosarcoma and endothelioma may be of degree rather than of kind.

Cohnheim found a case of leukemia without leukemic changes in the blood; he originally suggested the name "Pseudoleukämie," in 1865. Since that time the term has at times been applied to cases of Hodgkin's disease. Warthin described the condition as a generalized (or localized) aleukemic lymphocytoma; Ewing considered it a systemic aleukemic lymphomatosis; Sternberg emphasized certain features and separated it from true Hodgkin's disease; Cabot described it as "a hyperplasia of specially hemopoietic tissue closely akin to leukemia, in fact, distinguished therefrom solely by the absence of leukemic changes in the peripheral blood." Symmers readily separated the two diseases microscopically.

The general trend of feeling is that pseudoleukemia is a faulty term and should no longer be employed. This is to be especially emphasized here, as the relationships of Hodgkin's disease are obscure enough without further ambiguity.

Relation to Syphilis.—Although a number of references have been made to the relationship of syphilis and lymphogranuloma, cases in which the two conditions are present tend to be isolated and are really no more frequent than might naturally be expected with any other disease. There is a large preponderance of negative over positive serologic findings: Cunningham, 7 cases, all negative; Baldridge and Awe, 46 cases, 3 positive; Simmons and Benet, 16 cases, 3 positive; Wallhauser, 25 cases, 2 positive; Burnam, 173 cases, 1 positive. Of a total of 268 cases, therefore, 9, or 3 per cent, were positive, which is a fair average for any group.

MacCallum, after a minute search, using Levaditi's method, found no spirochetes. The spirochetes described by White and Proescher have never been accepted although several workers have attempted verification; the general opinion is that the so-called spirochetes are but con-

nective tissue fibers. Löwenbach cited an instance of Hodgkin's disease with syphilis. Treatment brought about recovery. Jordan, Schamschin and Staroff reported a case in which the gross findings at autopsy did not separate Hodgkin's disease from syphilis, microscopic examination being necessary to show that the supposed gummas were really lymphogranulomatous nodules. I have seen a similar case. Simmons investigated the cases of Gowers, Hutchinson, Renvers, Vaquez and Bibierre, Iwanow, Fabian, Kawatsare and Roth. In none of them was there satisfactory evidence of the implication of syphilis in the development of Hodgkin's disease.

Relation to Mycosis Fungoides.—A relation of mycosis fungoides to Hodgkin's disease was suggested many years ago. Lerrede said that the problem of the two diseases is the same, and Ziegler believed that the entire disease picture of mycosis fungoides is only that of a variety of species of Hodgkin's disease, and that they are either very closely related or identical. Paltauf, Louis Berger, Wechselmann, Hazen and Strobel (who included a review of the literature) and others were impressed by the possible identity or relationship of the two. Ketron, Gillot, Cornill and Renvier, and Pardee regarded mycosis fungoides as a lymphadenosis. Ceelen and Zurhelle described mycosis fungoides with visceral lesions. Arndt and Arzt separated the two, as did Berger and also Pardee and Zeit.

Vasiliu and Goia described an interesting case in which the clinical manifestations were those of mycosis fungoides and biopsy showed typical Hodgkin's disease. They followed Ranvier's belief, expressed in 1869, that mycosis fungoides is to be considered as a cutaneous form of Hodgkin's disease. However, they considered the term mycosis fungoides as too comprehensive, embracing several distinct conditions, as at one time the term pseudoleukemia did. Regarding this, Udo Wile (discussing a paper by H. E. Miller) stated that "mycosis fungoides is a useful clinical term and should be retained to differentiate tumors that tend to slough." Dühring, in 1888, referred to the condition as an "inflammatory fungoid neoplasm," which appears to apply to the clinical picture even today. He was impressed by the early inflammatory symptoms and later by the developments of a sarcomatous aspect.

Fraser considered mycosis fungoides to be a reticulum cell sarcoma of the skin and presented 2 cases in which the changes were unquestionably neoplastic. He brought evidence to show the genetic relationship between mycosis fungoides, lymphatic leukemia and lymphosarcoma. The suggestion to call lymphosarcoma a reticulum cell sarcoma is based on the assumption that the lesion in the skin has its origin in the reticulum cells of the papillary layer, the reticulo-endothelial system of the skin.

In connection with lymphosarcoma, Breakey cited a case of mycosis fungoides in which the two conditions were found together.

Keim classified mycosis fungoides with the true lymphadenotic infiltrations of the skin, including leukemia, lymphosarcoma, Hodgkin's disease, Sternberg's leukosarcoma and Kaposi's lymphoderma perniciosa. He held that the multiple clinical pictures associated with these diseases should be regarded as the variable expressions of the lymphoblastomas. In this connection McCarthy aptly remarked that "mycosis fungoides passes through so many different stages and shows so many phases of each state that it is not surprising that it may simulate very closely a large group of diseases at one time or another." This statement in my opinion also applies at times to true Hodgkin's disease.

No mention is made in the literature, to my knowledge, of mycosis fungoides in children. Borsutzky and Corbrille did not mention it, although cases of Hodgkin's disease in children are numerous.

Concerning the bacteriology of mycosis fungoides, Ausspitz reported a micrococcus; Vidal and Perrin, a staphylococcus; Rindfleisch, a micrococcus (in blood culture); Kubel, during life, a bacillus, and after death, a staphylococcus; Chevrel, a nonacid-fast, gram-negative cocco-bacillus; Verfasserin, from blood and tissues, both living and dead, an acid-fast rod that quickly became transformed into a nonacid-fast, gram-positive coccus. Busni reported the finding of a peculiar organism in 5 cases of mycosis fungoides and in 140 cases of lymphogranulomatosis. This bacterium in culture at first showed acid-fast forms, later appearing as a coccus, resembling Staphylococcus. This coccus did not return to the acid-fast form in vitro but had to be passed through an animal before it could be recovered in acid-fast form, and constitute constant findings. Busni regarded mycosis fungoides and lymphogranuloma as closely related, and both as bacteremias.

Differentiation between mycosis fungoides and lymphogranuloma is at times difficult (Fox; Ziegler; Miller). This may be true also on microscopic examination. McCarthy discussed this question in some detail. In typical cases of lymphogranuloma in which there is granulation tissue with numerous Sternberg giant cells the diagnosis can be made without difficulty. When these cells are absent, however, it may be almost impossible to separate the two conditions. In such cases the following considerations may be of value: In mycosis fungoides, in the eczemoid and beginning infiltration stages, in addition to the general findings, one may see many large lobulated, polymorphonuclear cells which are very similar to the Sternberg cell. However, in the tumor stage these cells are practically absent, which is in sharp contrast to the finding of large numbers of Sternberg cells in the tumor stage of lymphogranulomatosis. In mycosis fungoides the pleomorphism of the cell picture is most marked in the first stages, while in the tumor stage

the infiltrate has a more uniform make-up, being almost entirely composed of lymphocytic elements and connective tissue granulation cells. In the tumor stage the glands and internal organs show large numbers of eosinophils. Such a finding is absent in Hodgkin's disease. McCarthy further differentiated leukemic processes by the purely lymphocytic character of the infiltrate, by the absence of connective tissue proliferation and by the findings in the blood. Gans also differentiated lymphogranulomatosis and mycosis fungoides microscopically. In lymphogranulomatosis the nuclear and protoplasmic detritus is not found as in mycosis fungoides; moreover, the lesions undergo regression by caseation and necrosis, while in mycosis fungoides they disappear by absorption without caseation.

The question of a relationship between lymphogranulomatosis and mycosis fungoides must remain open. Certainly the clinical diagnosis of mycosis fungoides is frequently difficult or impossible, even for the most expert workers. I feel that Vasiliu and Goia have placed an interpretation on this relationship that harmonizes with the known facts very well—that mycosis fungoides is too comprehensive a term, embracing possibly several distinct conditions, but that a certain number of cases of what is commonly called mycosis fungoides must be considered as cutaneous forms of lymphogranulomatosis. In the latter statement they agree with Paltauf, Unna and Louis Berger. Until absolute criteria can be established for both diseases the question must remain open. Two recent cases reported by Milian illustrate this: The clinical diagnosis was mycosis fungoides, but on histologic examination of enlarged nodes, a diagnosis of lymphogranuloma was made. Markowitz made an interesting clinical comparison of the two diseases.

Relation to Myeloid Leukemia.—The possible relationship between lymphogranuloma and myeloid leukemia has been given some attention. Symmers stated that Hodgkin's disease and myeloid leukemia "are probably different quantitative responses to the same type of provocative agent," which is in accord with his theory that Hodgkin's disease has its origin in the bone marrow. In this connection Medlar's megakaryoblastic theory seems to require consideration, but at present no definite statement can be made. To those who hold to the infectious and also to the tuberculous nature of the disease, the work of Marshall and that of Twort may be stimulating. Marshall described a case of acute military tuberculosis showing the blood picture of myeloid leukemia. Twort inoculated 12 guinea-pigs with leukemic tissue and found that 6 had tuberculosis as a result.

Relation to Lymphatic Leukemia.—Cases have been described involving an apparent transformation of Hodgkin's disease into lymphatic leukemia (Wende; Warthin; Bunting and Yates). Burnam, who cited

173 cases of Hodgkin's disease, had never seen this occur, and he expressed the belief that the two diseases were quite different pathologic states. Richter's case of generalized reticular cell sarcoma of the lymph nodes was associated with lymphatic leukemia. He interpreted this as representing a leukemia of long standing, undiscovered, with the development of a rapidly growing malignant tumor superimposed. This explanation is stimulating when applied to the same problem in Hodgkin's disease. MacCarty's cytologic studies led him to believe in a close relationship between lymphatic leukemia, lymphosarcoma and Hodgkin's disease. Chute placed Hodgkin's disease, lymphosarcoma, lympho-epithelioma and leukemia under the name "malignant lymphoma," agreeing with the concept that these are but different forms of the same disease.

In conclusion, I again stress Ewing's view that strict adherence to histologic distinctions should be maintained, certainly in the absence of any known etiologic agent.

Relation to Tuberculosis.—The question of a relation of lymphogranuloma to tuberculosis is still highly unsettled, and discussion of it constitutes a considerable portion of the literature. The reports are so variable, and at times so entirely contradictory, that it is difficult to place them in an orderly and correlated sequence. I have therefore attempted to reduce the several phases of the question to statements of a categoric nature, referring to such articles as may bear on each division.

Rolleston presented the historical developments of the general knowledge of lymphogranuloma and briefly considered the possible etiologic relation to tuberculosis. Morgagni, in 1769, undoubtedly knew of the condition, but necessarily confused it with other lymphadenopathies. In Hodgkin's own series of 7 cases, Fox recently found unquestionable evidence of tuberculosis of the lymph nodes. Dickinson, in 1878, was the first to indicate that in cases of lymphogranuloma the tubercle bacillus may be considered as a secondary invader, but the modern controversy actually began with Sternberg's publication in 1898, in which he considered lymphogranuloma as a peculiar form of tuberculosis, in much the same way that lupus is a cutaneous form of tuberculosis, a view that has been actively supported and combated ever since. Sternberg has somewhat altered his contention at times, but he recently reaffirmed his original theory. Fraenkel and Much's finding of what they considered a granular form of the tubercle bacillus gave added strength to Sternberg's views, although many authors, notably Twort, have questioned both the presence and the significance of these granules. Animal inoculation has played a considerable part in the various attempts to decide the question, but the results are most confusing. Recently the problem has been brought to the fore by the negative find-

ings of Twort, the work of Vasiliu in support of Sternberg's theories, the immunologic studies of Stewart and Doan and the suggestion by L'Esperance that the disease may be caused by the avian tubercle bacillus.

In addition, a large amount of work has been done in investigation of the life cycle and of the possibility of a filtrable form or product of the tubercle bacillus, which to some observers is of importance in this connection. Other points will be considered later.

The various phases of the general relationships between lymphogranuloma and tuberculosis may be categorically stated in an affirmative sense as follows:

1. Lymphogranuloma is of tuberculous origin and represents a peculiar and atypical reaction of the host to the human type of *B. tuberculosis* or to a peculiar form of the same, as typified in the original view of Sternberg.

2. Lymphogranuloma and tuberculosis, either healed or active, are often found in the same patient (Ewing).

3. There is frequently a strong family history of tuberculosis.

4. Patients with lymphogranuloma often present tuberculous stigmas and lesions.

5. Acute tuberculosis often develops terminally in cases of lymphogranuloma.

6. Acid-fast rods, closely resembling *B. tuberculosis*, are found in lymphogranulomatous nodes (Sternberg).

7. Much's granules are found in lymphogranulomatous tissue and represent a form of *B. tuberculosis* (Fraenkel and Much).

8. Animals inoculated with lymphogranulomatous material will succumb to tuberculosis, which may be typical or atypical (Sternberg; Fraenkel and Much).

9. In acute tuberculosis, lesions are sometimes seen that are much like those of typical lymphogranuloma (Medlar and Sasano).

10. The hyperplastic form of lymph node tuberculosis may be almost indistinguishable from lymphogranuloma microscopically (Karsner; Rolleston).

11. Tuberculosis is a secondary invader in cases of lymphogranuloma, and is not etiologic (Dickinson; Longcope).

12. Tuberculosis finds in patients with lymphogranuloma a soil that is favorable for its development (Gilbert and Weil).

13. There is a facultative symbiosis between *B. tuberculosis* and the unknown etiologic agent of lymphogranuloma (Hirschfeld).

14. Avian tubercle bacilli are etiologic (L'Esperance).

15. The patient's capacity of reaction to the toxin of *B. tuberculosis* is the chief factor in the production of lymphogranuloma (Näslund).

16. Lymphocytes act on the tubercle bacillus, so altering its power of producing the classic picture of tuberculosis that instead it produces the peculiar histologic process of lymphogranuloma (Lichtenstein).

17. Lymphogranuloma may be produced by the "filterable elements of the tuberculous virus" (Martinoli).

18. Lymphogranuloma may be due to a degenerated form of *B. tuberculosis*, in which "this degenerate perhaps passes over into a diphtheroid type that is practically a distinct species." The disease is caused by this organism only in a particular type of host (Sweany [this view is no longer held by him]).

19. Lymphogranuloma causes an anergy whereby the patient's reaction to tuberculin is rendered negative, even when tuberculosis is present (Morquio).

20. The occurrence of lymphogranuloma and tuberculosis in the same patient, the tuberculosis being of the terminal generalized type, may be explained by the view that lymphogranuloma favors tuberculous infection or activates it when latent (Rolleston).

21. Lymphogranuloma is unlike tuberculosis in that it is not transmissible by methods used at present (Longcope; Stewart and Dobson; Cunningham and McAlpin; Twort; Tyzzer).

22. Occasionally in guinea-pigs inoculated with lymphogranulomatous material tuberculosis occurs showing lesions closely resembling those of lymphogranuloma. These lesions are atypical lesions of true tuberculosis (Schütt).

23. Lymphogranuloma is unlike tuberculosis in that family histories of lymphogranuloma are exceedingly rare.

24. The reaction to tuberculin in patients with lymphogranuloma is uncertain.

25. Tubercle bacilli, probably bovine, may be demonstrated in lymphogranulomatous material by repeated passage through guinea-pigs (Sticker).

26. Lymphogranuloma is a tumor process in which tuberculosis plays the part of an excitant (Stahr).

27. Lymphogranuloma is an expression of an atypical tuberculosis produced by toxins from inert or nonextending foci. The tuberculosis sometimes seen late in the disease may be a flare-up of this focus or a return to type of an atypical lesion (Paisseau, Valtis and Saenz).

The possible etiologic significance of the human tubercle bacillus in lymphogranuloma has been considered affirmatively by Sternberg, Crowder, Ferrari and Comotti, Steinhaus, Schur, Türk, Hitschman and

Stross, Fraenkel and Much, and more recently by Vasiliu and Goia. It may be stated that definite proof is lacking, not only in this but in many of the other divisions listed. Briefly, the evidence used in support is as follows: The histologic appearance of lymphogranuloma is not incompatible with an infection such as tuberculosis, and furthermore is that of a granuloma; giant cells similar to those in lymphogranuloma are seen in certain lesions of tuberculosis; acid-fast rods are present in some cases of lymphogranuloma; Much's granules are seen in some cases of lymphogranuloma; inoculation with lymphogranulomatous material frequently causes tuberculosis in animals; lymphogranulomatous patients often present tuberculous stigmas and lesions and have family histories of tuberculosis; the two diseases are often found together in the same patient, and generalized tuberculosis may often develop terminally; by repeated passage of lymphogranulomatous material through guinea-pigs, tubercle bacilli, probably of the bovine type, may at times be demonstrated; avian tubercle bacilli are claimed to have been demonstrated by inoculation of animals and fowls with lymphogranulomatous material.

All of these points have been questioned, and some of them absolutely contradicted. Clarke began the active discussion against this view, and many others have carried it on (Reed; Longcope; Simmons; Fischer; Butlin; Yamasaki; Schottelius; MacCallum; Duval and Howard; Twort; Terplan and Mittelbach; Fox and Farley; Baldridge and Awe; Frates and Galli; Sussig; Lange and others). The most exhaustive recent report is that by Twort, who attempted to duplicate the work of Fraenkel and Much, but who had decidedly negative results.

It is true that lymphogranuloma and tuberculosis are found together in the same patient, and Ewing's well known statement that "in New York where the disease is very common tuberculosis follows Hodgkin's disease like a shadow" must be given due weight. Sternberg and others found this combination commonly. Ziegler obtained family histories of tuberculosis in 10 per cent of cases, and found the diseases co-existent in 20 per cent. Lemon cited 191 cases of lymphogranuloma, with clinical tuberculosis in but 8 cases; Schreiner and Mattick, with 46 cases, and Burnam, with 173 cases, found the combination very infrequently. Baldridge and Awe noted it in but 2 of 46 cases, and found active fibrocaseous tuberculosis in none of 150 cases of "lymphoma." I have encountered clinical tuberculosis in but 2 of over 30 cases. To carry the investigation further, I examined 151 autopsy reports from the literature: Tuberculosis, active or healed, was present in 31 cases and absent or not demonstrated in 120. This gives an average of about 25 per cent, a little higher than Ziegler's 20 per cent.

Recently Parker, Jackson, Bethea and Otis analyzed an extensive series of cases in which autopsy was performed and offered statistics in

support of the close association of the two diseases. Healed and active tuberculosis is "significantly greater in Hodgkin's disease (33.3 per cent) than in other types of lymphoma (5.3 per cent) or in cancer (14.6 per cent) or general autopsies (19.3 per cent)." They emphasized their finding that "malignant lymphoma of other types (not Hodgkin's disease) is never associated with active tuberculosis."

A comparison of the incidence of tuberculosis among the public at large with tuberculosis as seen in patients with lymphogranuloma may be of value here. Baldwin, Petroff and Gardner drew conclusions from a number of extensive surveys and stated that in large numbers of people, 1 per cent have active tuberculosis and 1 per cent have recognizable but arrested tuberculosis, or that 2 per cent have demonstrable lesions. Rokitsansky long ago demonstrated tuberculosis in a large percentage of routine autopsies. The results of the von Pirquet test as performed on the general public show about 90 per cent positive reactions. Another feature of interest is the demonstration by Gardner that tuberculous lesions may resolve, heal and disappear. In this laboratory at autopsy tuberculosis has been grossly demonstrable in 36 per cent of cases in general during a period of fifteen years.

These figures are compatible with those given in a preceding paragraph for lymphogranuloma. In 267 cases of lymphogranuloma, tuberculosis was demonstrable clinically 12 times—i. e., in 4.5 per cent—and tuberculosis, healed or active, was demonstrated post mortem in 25 per cent of 151 cases of lymphogranuloma in which autopsy was performed. Active terminal tuberculosis, however, especially in the generalized form, is a not unusual finding, and really should be considered separately. The results of tuberculin tests are not parallel, as negative reactions apparently preponderate in the presence of lymphogranuloma, which recalls the occasional negative reactions in the presence of unquestionable tuberculosis: the relationship remains obscure. Regarding the coincidence of tuberculosis and all forms of malignant growths, Fortune found in the examination of lengthy series of records that active tuberculosis is combined with malignant growths in about the same number of cases as with any other major fatal disease, and that healed tuberculosis is present in about the same number of cancerous as of noncancerous patients. Simonds found that sarcoma combined with tuberculosis in the same patient was reported rarely. I fully realize that fallacy occasionally results from reasoning on the basis of statistics, but the percentages cited for tuberculosis and for lymphogranuloma appear sufficiently close to indicate that tuberculosis occurs with lymphogranuloma in considerably fewer cases than has been commonly supposed, and that the coincidence approaches the normal expectancy. It is unfortunate that large numbers of completely detailed clinical and autopsy reports

of cases of lymphogranuloma are not available for analysis; only by such study can a true comparison be established, clarifying this debated matter.

The question naturally arises as to the possibility of overlooking tuberculous lesions in the presence of a preponderating and closely simulating mass of lymphogranulomatous tissue. Lubarsch showed that B. tuberculosis may be detected by animal inoculation in the absence of grossly demonstrable tuberculosis. Clinically this is, of course, easily possible, and even at autopsy it is understandable. Of interest in this connection are the reports of Schütt and Sweany, both of whom found minute, single, isolated tuberculous lesions, and also those of Kusunoki and Ewing, who found tuberculosis in single lymph nodes immediately adjacent to typical lymphogranulomatous nodes. The significance of these observations cannot be overestimated, for without such painstaking search the tuberculous lesions would undoubtedly have been missed and the patients described as free from tuberculosis, yet animals inoculated with material from them would conceivably have shown tuberculosis. Barron's statement is pertinent in this respect, that possibly glandular tuberculosis is more common in some locations than in others, which would serve to explain the markedly positive results of inoculation obtained by Sternberg, Fraenkel and Much, and others, in contrast to the negative results of Twort, Terplan and Mittelbach, and others. Not only may this remark be true, but many of the positive results may be analogous to those in the cases just mentioned in which undiscovered tuberculosis was present, and so accounted for the positive results of inoculation. Kaufmann has called attention to the possible accidental and unavoidable admixture of lymphogranulomatous and tuberculous tissue.

Another group of papers of similar significance includes those of Loomis, Opie and Aronson, Pizzini, and Kälble, Macfayden and MacConkey, who showed that "normal" lymph nodes frequently contain living tubercle bacilli capable of producing tuberculosis in animals. Bloomfield found numerous bacterial forms in normal lymph nodes, and Twort stated that although lymphogranulomatous nodes might contain tubercle bacilli, they perhaps as frequently contained streptococci or diphtheroids. Certainly with these facts in mind, animal inoculation experiments seem to lose much of their value in this problem.

Bovine tuberculosis has been suggested by Sticker, who used repeated passage through animals to demonstrate the organism. Lanken described canine tuberculosis in which enormous numbers of acid-fast rods were found in the mesenteric lymph nodes, the histologic picture of which resembles closely that of lymphogranuloma. These organisms could not be cultured, and they showed decreased pathogenicity on repeated passage through animals. I encountered a case of bovine

tuberculosis involving the hip joint in which well defined and generalized lymphogranuloma was a later development.

Avian tuberculosis has recently been advanced by L'Esperance as an etiologic possibility. Essentially the evidence in favor of this is: 1. Chickens inoculated with lymphogranulomatous material show typical avian tuberculosis, and inoculation of material from these chickens into other chickens causes a more marked and extensive tuberculosis with involvement of the bones. Cultures of material from the second group of chickens give a pure growth of culturally avian tubercle bacilli. 2. In guinea-pigs treated with killed human tubercle bacilli prior to inoculation with lymphogranulomatous material, an atypical tuberculosis of the lymph nodes develops and cultures on egg medium show many characters of avian tubercle bacilli. 3. Subcutaneous inoculation of rabbits with original lymphogranulomatous material causes no infection, as frequently happens with pure cultures of avian tubercle bacilli. The conclusion drawn from these experiments is that "this may indicate that the etiologic agent in certain forms of Hodgkin's disease is pathogenic for birds, or that the avian tubercle bacillus is a factor in producing some of the lesions which are interpreted as Hodgkin's disease." Utz and Keatinge attempted to confirm this work and were inclined to believe in the etiologic rôle of a bacillus closely resembling the avian type of tubercle bacillus. Branch, however, could not come to this conclusion. He included an extensive survey of avian tuberculosis. In an article on avian tuberculosis in rabbits, Medlar stated that the presence of myeloid giant cells, which are megalokaryocytes, in the spleen, liver and lungs, suggests a similarity between the process and Hodgkin's disease. Mayo and Hendricks described 2 cases of avian tuberculosis in man, in both of which the patients recovered following splenectomy. Other cases of avian infection in man have been noted occasionally. Baldwin, Petroff and Gardner stated that there has been a considerable increase of tuberculosis in chickens during recent years, which must be considered in experiments in which these birds are used. Petroff also hesitated to designate the avian tubercle bacillus as a true separate strain. Avian tuberculin has been used both as a test material and therapeutically.

In the course of my own work, 6 chickens inoculated with lymphogranulomatous material did not show tuberculosis after several months' observation. Nocard, and later Wiener, rendered human and bovine tubercle bacilli virulent for chickens by placing the cultures in colloidal sacs and enclosing these in the peritoneal cavities of hens. The sacs were removed after several weeks, cultured on potato and again placed in the peritoneal cavities of hens. After three passages they had become sufficiently virulent to infect a chicken seriously. Bang also observed the apparent transformation into avian tubercle bacilli.

Stewart and Doan used the phosphatid fraction of the lipoids of the tubercle bacillus as an antigen in testing serum from tuberculous patients, the test being a precipitin reaction. In 9 patients with lymphogranuloma on whom the tests were made, "the presence of free phosphatid-antigen was suggested in tests with antisera for avian phosphatid, four of the cases giving also a positive precipitin reaction with antihuman tuberculo-phosphatid serum. This observation would lend support to L'Esperance's finding of the avian tubercle bacillus in certain Hodgkin's cases." This work should be of interest to all students of the disease, especially as it presents a new avenue of attack.

The possibility that the disease may be due to an atypical, degenerate or other altered form of *B. tuberculosis* has been widely discussed since Sternberg's first report. Weigert, in 1884, demonstrated in lymphogranulomatous nodes organisms that resembled the tubercle bacillus; Fraenkel and Much believed that Much's granules were really the granular form of *B. tuberculosis*. Kahn observed in vitro the development cycle of a single tubercle bacillus and described forms that resemble diphtheroid bacilli morphologically, coccoid types and granular, nonacid-fast forms that closely resemble the granules of Fraenkel and Much. Sweany had already recognized mutation forms, much the same as those seen by Kahn; he suggested that the diphtheroid bacilli of Billings as well as the granular forms of Fraenkel and Much may be degenerated tubercle bacilli. He described the isolation of two types of acid-fast bacilli from the same case: a "smooth" moist type resembling the avian variety, but avirulent for all common animals (including chickens) except guinea-pigs, in which large doses produced death with a tuberculosis-like pathologic picture, and a second type which was unstable at first but which became like the human type. Twort attempted to heighten the virulence of certain acid-fast bacilli, especially *Mycobacterium phlei*, with negative results. The virulence was not affected by injection of lymphogranulomatous, cancerous or leukemic tissues. He further found that lymphogranulomatous material in fluid culture mediums had no noticeable effect on the surface growth of *B. tuberculosis* and allied saprophytes. The peculiar organism described by Busni, while not believed to be the tubercle bacillus, somewhat closely resembles it. The possibility of a filtrable form was considered by Vasiliu and Goia and by Martinolli. It is questionable whether there is a true filtrable form, according to several writers. Gloyne, Glover and Griffith stated that Fontès, in working with Much's granules, first suggested the possibility; they concluded, however, that a filtrable form does not exist.

Probably a majority of students of the disease (notably, Reed, Longcope, Lemon and others) have considered *B. tuberculosis* as a secondary invader. This view is tenable, although it is not proved,

especially when the great incidence of tuberculosis is realized, more particularly the healed and quiescent types containing viable tubercle bacilli. If it is true, as many believe, that the lymphoid and reticulo-endothelial systems are concerned in the defense against tuberculosis, it is hardly surprising that a lighting up of a tuberculous focus should occur when these systems have been practically eliminated or seriously injured by a disease such as lymphogranuloma. The duration of viability of the bacilli after growth has ceased, as in healed lesions, is not known, but in artificial cultures it generally is less than two years. In the body it must be much longer, if only to account for the facts as seen in lymphogranuloma. The most usual active tuberculous lesion found in lymphogranuloma is the acute miliary or submiliary type occurring late or terminally, which is compatible with this theory.

The histologic relationships were considered under the heading of histology, to which the reader may refer. Reference may also be made to the section on tuberculin tests.

Space will not permit a more extensive discussion of this highly important aspect, for the material already at hand could easily be made to yield a sizable monograph. One of my chief objects in offering this somewhat extended presentation was to call attention to the numerous and complex ramifications of what at first appears to be a direct question of etiologic relationship. It is evident that it is much more.

Tuberculin Tests.—Tuberculin tests have given uncertain results. Positive results were obtained by Biuclic, Baumler-Diehl, Halstead, and Simmons; negative results by Beitzke, Weill and Lesieur, Simmons, Lehndorf, Osler, Reed, Ruffin, and Sauler. In 2 cases in which pleurisy was present, Morquio reported 2 negative results. Borsutzky found the von Pirquet test negative in two thirds of cases in children; Corbeille corroborated this, saying that in none of his cases were there definitely positive results. MacNalty gave the patient in his case 0.00005 mg., which he increased to 0.0001 mg., every ten days with no effect. Rulison reported the use of three types of tuberculin; with the avian and the human type the reaction was positive, and with the bovine type it was negative; he suggested a possible skin test. It is interesting to note that a node from this patient was injected into a chicken, with no apparent effects in nine months of observation.

In a case which I recently observed old human tuberculin was used intracutaneously. The injection (0.01 mg.) was followed shortly by a profound constitutional reaction—rise in temperature, etc. Furthermore, on several subsequent occasions the same reaction occurred following similar injections. The histologic picture of a previously excised node was that of Hodgkin's disease and in no place did it suggest tuberculosis, the diagnosis being agreed on by three pathologists. From a clinical point of view, this could be interpreted only as a specific

reaction. The enlarged nodes decreased a little in size, but at no time presented the appearance of tuberculosis. I have noted but one other definitely positive reaction to tuberculin in a series of more than 30 cases. This occurred in a child who had tuberculous arthritis of long standing plus Hodgkin's disease. A positive, though not a marked, reaction was obtained with bovine tuberculin (intracutaneous injection). Tyzzer reported a negative reaction to tuberculin in a monkey which had been inoculated with an emulsion of tissue from Hodgkin's disease. White and Fox reported tests on 12 normal monkeys, with 37 per cent positive results. Morquio, in discussing the commonly negative results of the tuberculin test in Hodgkin's disease, stated "that lymphogranulomatosis causes a condition of anergy of the patient, by which the reaction to tuberculin is rendered negative, even when tuberculosis is present."

MEDICOLEGAL ASPECTS

Four cases present certain features of possible medicolegal interest involving trauma. One of these was reported by Hirsch: A man fell and fractured five ribs, which caused two months' disability. Six months later his condition was diagnosed as lymphogranuloma. Hirsch stated that the accident excited or stimulated a possibly preexisting lymphogranuloma of the hilar lymph nodes. The patient in Hendrick's first case injured both arms and the lower ribs. After some time enlarged nodes were seen, and biopsy showed Hodgkin's disease. The patient in Hendrick's second case fell, experiencing pain in the inguinal region, abdomen and chest. On examination, an inguinal hernia was found, and operation was performed. A short time later the patient complained of pain in the splenic region. An irregular fever, anemia and enlargement of the lymph nodes and spleen developed, with dulness over the base of the left lung. Death occurred three months after operation. Autopsy showed Hodgkin's disease. Hendricks claimed, however, that the trauma had no causal relationship, although both of his patients drew workmen's compensation. His second case presented other unusual and interesting features of a medicolegal nature. One of my cases had its onset just after an accident. A young woman injured her thigh. This was followed by enlargement of the inguinal lymph nodes and then by the development of a rather large pelvic mass. Two well qualified pathologists considered that the biopsy showed Hodgkin's disease, but I have always believed that the condition was sarcoma. Death was preceded by generalized enlargement of the lymph nodes.

CLINICAL AND GENERAL PATHOLOGIC ASPECTS

Although in this review adequate consideration cannot be given to the purely clinical phases of the disease, a number of interesting and

unusual observations encountered in the literature may be mentioned. The field of pathology has already been covered by numerous authors and has received attention under various subheadings in this review. A few reports of particular interest are included here.

MacNalty's detailed work on the peculiar pyrexia is of importance; Rolleston supplemented this and included a special bibliography. In Abrahams' case the condition closely resembled typhoid, a finding occasionally mentioned by others (Ziegler; Muller and Boles; Weiss; Isaacs). Creevy took up the question of irregular fever in general, and found that this type was not confined to lymphogranuloma but occurred especially in hypernephroma. Barron's case 1 showed a curious cyclic fever with intervals of three weeks, which suggested an infection with an animal parasite. He mentioned the rarity of this type of fever and cited MacNalty, Whillington, and Longcope as having seen similar cases. Abrahams cited a case with periodic pyrexia. Subnormal temperature was noted in a case by Simmons and Benet. Cunningham found normal temperatures in 13 cases during the period of observation. Fabian found the Pel-Ebstein type of fever in 50 per cent of cases. Desjardins and Ford observed fever in 31.3 per cent of a series of 135 cases. Barron found fever in about 50 per cent of 24 cases. Jackson contributed information on the occurrence of fever.

Odd manifestations have occasionally been encountered: subcutaneous emphysema (Baldrige and Awe); tachycardia of persistent rate (Dumas, Bernay and Boucaumont); paroxysmal abdominal pain (Fox and Farley; Whillington); backache as an early symptom (Isaacs); albuminuria without lymphogranulomatous lesions in the kidneys (Vasiliu and Goia); perforation of an intestinal ulcer (McAlpin and Von Glahn); mild neuralgias as a common symptom (Burnam); paroxysmal tachycardia as the first symptom, due to fatty degeneration of the vagus resulting from pressure by a mediastinal mass (Graber; MacNalty; Murchison; Ebstein; Pel); epistaxis (Barron); vocal disturbances (Chatellier); involvement of the breasts (Marimón; Kückens; Kaufmann); corneal infiltration (Lagrange; Morax); orbital involvement (Reeves; Simmons and Benet); perforation of the wall of the chest (Lyon); generalized miliary form (Gsell).

Clinical classifications in general follow Trousseau's earliest (1865) division into latent, progressive and cachectic stages. Ziegler's work is well known. Other studies are those of Cunningham, Vasiliu and Goia, and Favre. Symmers contributed a detailed paper on the clinical significance of pathologic changes, offering a division of the disease into two types, the ordinary and the invading.

Acute cases are not the rule but do occur (Karsner; Clarke; Kretz; Hirschfield and Isaac; Howell [reported a case closely simulating acute appendicitis]; Whillington; Cunningham). Clinical variation without

corresponding qualitative histologic changes was seen in acute and chronic cases by Baldrige and Awe. In their opinion, acuity tended to have an inverse relationship to the age of the patient.

Jaundice occasionally occurs as a symptom (Pepper; Longcope; Gsell; Coronini; Barron [who found peribiliary infiltration at autopsy]).

Conditions simulated by lymphogranuloma and thus confusing the diagnosis are numerous. This phase has been discussed by Whitaker, Baldrige and Awe, and Holler and Paschkis, who reported an unusual case simulating hemolytic jaundice.

Recession in the size of the enlarged nodes was commented on by R. C. Cabot, who found it in the nodes and in the spleen when an acute infection occurred during the course. I have seen it occasionally following diagnostic biopsy. Messick and Furrer reported the absence of any enlargement of the superficial or mediastinal lymph nodes in the presence of a retroperitoneal involvement.

TREATMENT

Surgical Treatment.—There are advocates for and against the surgical removal of lymphogranulomatous tissue. Yates, and Yates and Bunting spoke in favor of radical operative treatment, especially in cases showing single rather than multiple distribution. Larrabee cited a case in which splenectomy was performed with good results, there being but small nodes in the neck. Tandberg described resection of the upper lobe of a lung, followed by roentgen irradiation. Minot and Isaacs, in evaluating the results of surgical treatment alone or plus irradiation and of irradiation alone in cases of lymphoblastoma, stated that in patients treated by surgical intervention, whether irradiation was used or not, the average duration of life following treatment was 3.67 years, 1.11 years longer than the average of 2.56 years without this treatment. They suggested that surgical procedures are most likely to be used when the disease seems to be localized, has progressed slowly or is not extensive. "It is just such cases that seem by nature to be destined to last relatively long." Burnam stated that surgical intervention alone has no value aside from furnishing biopsy material, and that extirpation not followed by roentgen irradiation usually means rapid recurrence. Sussig was in full accord with him in this, but put emphasis on radical surgical intervention and on medical treatment as well as on irradiation. Borsutzky, and Fischer expressed themselves as against surgical treatment, considering it useless and productive of acute recurrences. I had a patient who showed marked enlargement of the right side of the neck within a few days after a radical extirpation on the left side of the neck. Cases are recorded, however, in which this did not occur. Muller and Boles believed that radical operation is to be considered when external evidence indicates that the disease is chronic and nonprogressive, when

some function is interfered with by pressure, and when splenomegaly persists after irradiation. Weil advocated laminectomy in certain cases of spinal involvement.

Drugs.—Since Murchison, in the belief that the condition was a form of tuberculosis, treated a patient with quinine, iron and cod liver oil, numerous remedies have been tried. Some have apparently helped, and others have had no effect. Iodine, iron, phosphorus, colloidal metals, benzene, sodium salicylate, methenamine, emetine hydrochloride and emetine bismuth iodide have all been unsuccessful. The arsenicals have long been used—arsenic trioxide, colloidal arsenic trisulphide, sodium acetyl arsanilate, arsphenamine, neoarsphenamine, sodium cacodylate and sodium arsanilate. At times improvement or remission has been seen with the use of neoarsphenamine, and occasionally with some of the other arsenicals. No cures are claimed, however. Chevallier reported some palliative effects from the use of antimony, apparently better than those obtained with arsenic. Grasso could not obtain any effect with antimony. Acetylsalicylic acid is of value in controlling pruritus. Cod liver oil is used in the same manner as in tuberculosis. I used chaulmoogra esters in a case, but without success.

Biologic Preparations.—Erysipelas and prodigious toxins (Coley) have been tried with little effect or with results of doubtful value.

Ovarian extract was offered by Gemmell as a means of increasing resistance in females; he also used an extract of the lymphatic glands internally. This will be discussed further under gynecology.

Radioactive Substances.—Stevens claimed good results with intravenous injections of radium chloride. The use of thorium X subcutaneously and of thoron intravenously may be mentioned also. These substances must be considered as dangerous in view of the well known effects of radium poisoning, even when very small amounts are absorbed (Martland).

Ten Doornkaat-Koolman advocated repeated sojourns at high altitudes plus roentgen therapy; he obtained a remission of four years' duration in a case in which this treatment was used. Ernst attempted to adjust the patient's vitamin balance, in addition to giving roentgen therapy. It seemed that small doses of x-rays produced much more marked results when such a balance was effected. He used a diet rich in vitamin B, plus enemas containing *Bacillus tumefaciens*, chosen because of its high content of vitamin A. No claims were made as to cure.

Transfusions of blood have often been used for the anemia. Burnam, reporting 173 cases, stated that they should rarely be resorted to. Sharp reactions are frequent even when the blood is most carefully matched; death occurred in 1 case. My own experience is in agreement; I believe blood transfusions to have only transitory value.

Vaccine and Serum Therapy.—Numerous attempts have been made to use the diphtheroids isolated from the lymph nodes as vaccines. Billings and Rosenow, Hatcher and Lemon, Fox, Cunningham, Mellon, and Bunting and Yates reported variable results. After a fairly comprehensive review of the literature, the feeling is perhaps justified that bacterial vaccines of this type at times possibly produce remissions. Their action is too uncertain, however. One cannot lose sight of the important fact that remissions frequently occur without any treatment. This statement must always be considered in attempting to evaluate any therapy in Hodgkin's disease. Cunningham stated the general feeling toward vaccines of *C. hodgekini*: "They have had a fair trial, but since this organism is not the specific cause it seems futile and a waste of time and material to continue."

Lortat-Jacob and Schmite proposed the injection of the serum from an irradiated patient with Hodgkin's disease into another patient not yet irradiated, roentgen therapy being given after the injection. The erythrocyte count was definitely improved.

Schreiner and Mattick used autolyzed lymph nodes as a vaccine, with no results. Wallhauser and Whitehead used sterile lymph node filtrates, with variable effects; however, they apparently obtained remissions in some cases. Hanrahan, who used the same method, felt that possibly remissions were obtained at times. In a series of cases I noted effects which were favorable in some instances and distinctly unfavorable in others. No cures can be claimed. Grapiolo and Tenconi obtained favorable remissions through the injection of extracts of macerated glands.

Miller's report on 2 cases of Hodgkin's disease is most interesting; one of the patients was well for ten years following an attack of erysipelas; the other was moribund but recovered after an attack of severe gangrenous herpes zoster. The observations leading to the advocacy of erysipelas and prodigious toxins (Coley) are somewhat parallel. Certainly some profound reactions may at times initiate remissions which can hardly be coincidental in all cases and which appear at times to resemble those seen in sarcomatosis.

HODGKIN'S DISEASE IN LOWER ANIMALS

Few cases are recorded, possibly because of insufficient search. In investigating the Slys stock of mice, Simonds found 316 cases of enlargement of the lymph nodes and spleen in 15,000 autopsies. He found 4 mice which showed a condition closely resembling the disease as seen in man, although he refrained from making a positive diagnosis. The histologic picture generally was that of replacement of the lymphocytes by large cells. The spleen was enlarged; in 3 animals the liver showed periportal infiltration by lymphocytes and large cells, and in 1

there was a mass of the same cells in the hilus of the kidney. Krebs, Rask-Nielsen and Wagner recently undertook a study of lymphosarcomatosis in white mice which is of interest in attempting to correlate lymphosarcoma, leukosarcoma, lymphatic leukemia and lymphadenosis. They described a lymphatic leukemia in the mice which is transferable from generation to generation in strongly irradiated animals, and which may appear sometimes as lymphosarcoma, as leukosarcoma or as lymphadenosis. They suggested the name "lymphomatosis infiltrans (leukemica or aleukemica)" and believed that there is a close relationship between the disease in mice and that seen in man. The recent attention to avian tuberculosis gives interest to Ellermann's work on the leukemias of fowls. He stated that the chicken has no lymph nodes, and that the mass of apparent lymphoid tissue in the neck is really thymic tissue. Lanken described a case of canine tuberculosis with a nonculturable virus, in which the histologic picture of the lymph node closely resembled that of Hodgkin's disease. Many acid-fast rods were found, but they could not be cultivated, although a series of guinea-pigs into which they were injected were affected.

Other references to the disease in lower animals are given in the bibliography of Simonds.

DEATH

The manner and the time of death depend on several variable factors, chiefly the course (acute or chronic), the organs and situations involved, the degree of anemia, secondary infections, the quality of the patient's resistance and the treatment. The subject is therefore too extensive to be taken up completely here. A remarkable case of sudden death was described by MacCallum in discussing Paullin's paper. The patient had areas of softening in the ribs. "One day the patient was sitting up in bed and he leaned forward to drink a cup of tea, when he suddenly died." The autopsy showed that the odontoid process of the axis was completely severed by erosion, and the slight effort had dislocated the vertebral column so as practically to cut the cord in two. Cases of sudden death are numerous, but in none of those reported was death as instantaneous as in MacCallum's case. Some common causes of death are: suffocation as the result of a large mediastinal tumor pressing on the bronchi and trachea (Weber); generalized peritonitis from perforation of an intestinal ulcer in lymphogranulomatosis of the gastro-intestinal tract and acute anemia from hemorrhage (Hayden and Apfelbach); acute pulmonary edema; bronchopneumonia, and an acutely speeded up cachexia. Ginsburg correctly stated that in acute cases death usually occurs not by "a proliferative compressive phenomenon, but by a severe toxemia which presented all the characteristics

of an acute infectious disease." Heissan, Levy, Hendricks, Whillington and Howell cited acute cases that are of interest in this connection.

In chronic cases, the picture is somewhat different. The immediate cause of death varies with the case. Generally anasarca, delirium of varying degree, pleural effusion and icterus are symptoms that may immediately precede death (MacNalty). Cunningham stated that the final state may present a picture of acute toxemia with high intermittent fever, the temperature becoming subnormal for several days before death. I saw a case in which the patient remained fully conscious up to within two hours of death and 2 cases in which excessive irradiation unquestionably hastened the end. In one of these the patient was so severely burned that the anterior abdominal wall was partially necrotic. Another patient who had been in coma suddenly had a remission two days prior to death. He became fully conscious, strong and alert enough to sit up and shave himself; he then passed slowly into a progressive coma. No 2 cases are quite alike, and death unquestionably ensues from a variety of factors.

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Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—In the medical school of the University of Georgia a department of bacteriology has been established with James A. Kennedy at the head.

F. Blumenthal, director of the Institute for Cancer Research in Berlin, has accepted the appointment as professor in the faculty of medicine in Belgrade, where he will continue his experimental work in cancer.

Hans Zinsser, professor of bacteriology and immunology in Harvard Medical School, has been given the degree of doctor of science by Lehigh University.

George H. Hansmann, assistant professor of pathology in the University of Iowa, has been appointed associate professor of pathology in Georgetown University, Washington, D. C.

Frederick G. Novy has assumed the deanship of the medical school of the University of Michigan.

Twenty fellows are now working under the Medical Fellowship Board of the National Research Council.

Bernhard Zondek, whose name is associated with the hormone test for pregnancy, is now consulting gynecologist to the Victoria Memorial Jewish Hospital in Manchester, England.

Albert Calmette, assistant director of the Pasteur Institute in Paris and originator of the BCG vaccine against tuberculosis in infants, has died at the age of 70.

Friedrich Fülleborn, director of the Institut für Schiffs- und Tropenkrankheiten in Hamburg, well known investigator in tropical medicine, especially helminthology, died on Sept. 9, 1933.

Society News.—The Second International Conference on Geographic Pathology will be held in Utrecht, Holland, in July, 1934. The subject for discussion will be arteriosclerosis.

The American Association for the Advancement of Science will meet in Boston from Dec. 27, 1933, to Jan. 2, 1934.

The Society of American Bacteriologists will hold its thirty-fifth annual meeting in Philadelphia, Dec. 27 to 29, 1933, under the presidency of William Mansfield Clark.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE EFFECTS OF RADIUM IRRADIATION ON TISSUE CULTURES. W. G. WHITMAN, *Am. J. Cancer* **17**:932, 1933.

Tissue cultures were exposed to radium emanation in varying doses. Since most of the beta rays were eliminated by filters, the effects were due almost entirely to the gamma rays. The normal fibroblasts showed the characteristic fall and recovery in mitotic count after irradiation, depending on the dosage and the length of exposure. Cells in division at the onset of irradiation proceeded in a normal fashion to complete mitosis. Abnormal mitotic figures, consisting of pyknotic, shrunken and clumped chromosomes, were found shortly after irradiation. Scattered, aberrant and lagging chromosomes, with the formation of nuclear fragments and chromosomal vesicles, were also characteristic of irradiated cultures. It is suggested that possibly some of these changes during karyokinesis may be due to an injury or a change in the consistency of the spindle substance. No damage was observed to mitochondria or nucleoli following irradiation. Cultures of Walker rat sarcoma 338 were exposed to 5, 16 and 50 millicurie hours. Similar morphologic changes were noted, but such changes occur also in nonirradiated cultures. In addition, the irradiated tumor cultures appeared unable to live if the medium was changed after irradiation. The normal cells (macrophages) appeared to be more affected by these doses than did the tumor cells. The number of mitoses of the normal cells (macrophages) was proportionately more reduced by irradiation than that of the malignant cells. The percentage initial fall in the mitotic count for the normal cells was greater for all three doses than for the malignant cells.

AUTHOR'S SUMMARY.

A CLASSIFICATION OF THE DISEASES OF LIPOID METABOLISM AND GAUCHER'S DISEASE. LUDWIG PICK, *Am. J. M. Sc.* **185**:453, 1933.

The xanthomatoses are divided into two groups, namely, generalized and localized. The generalized forms consist of (1) the symptomatic or secondary forms, those which accompany other diseases and are manifestations of disturbances of lipid metabolism associated with these diseases, and (2) the essential or primary forms, those which constitute disease entities in themselves and are based on a constitutional anomaly of lipid metabolism. In this group belong (a) Gaucher's disease, (b) Niemann-Pick's disease (c) Hand-Schüller-Christian's disease and (d) the primary nonsymptomatic external and internal xanthomatoses which occur in varying distributions and intensity in the skin and in the internal viscera. The morphologic picture of Gaucher's disease consists of the deposit of the typical, large, fat-containing Gaucher's cells in the spleen, liver, lymph nodes and bone marrow, resulting in enlargement of the spleen and liver and in nodular or diffuse collections of cells in the marrow cavities, especially of the long bones. The Gaucher substance is optically and microchemically inactive. Mandelbaum's dictum, that a microchemical finding of neutral fat, myelin-like or doubly refractile substance in suspected cells excludes the presence of Gaucher's disease, still holds true. The Gaucher substance is essentially kerosin but contains phosphatides soluble in alcohol. The Gaucher cells arise from the reticulum cells of the spleen, lymph nodes and bone marrow as well as from the adventitial and periadventitial cells of the splenic arterioles. Pathogenetically, Gaucher's disease exemplifies a primary congenital and familial metabolic disturbance on a constitutional basis. The constitutional basis is indicated by the early onset, the familial occurrence, the predominance of the female sex and the susceptibility of the Jewish race.

SANDER COHEN.

PATHOGENESIS OF ERYTHROLEUCOSIS. H. L. RATCLIFFE and J. FURTH, with the assistance of C. BREEDIS, *Am. J. Path.* 9:165, 1933.

Under the influence of a filtrable agent, the basophil erythroblasts of the sinusoidal capillaries of the marrow undergo unrestricted multiplication. The erythroblasts thus formed fail to mature. They crowd out all other elements of the marrow, secondarily invade the circulation and accumulate in the capillaries of the internal organs, where they continue to multiply. Fowls inoculated with material containing erythroleukotic cells showed growth of the cells in the blood stream and the organs at a time when erythroblasts had only partly filled the capillary bed of the marrow. In fowls in which injections of the cell-free material had been made the blood did not contain these immature cells until the marrow was almost completely filled by them. With erythroleukosis, thrombocytes in the blood stream are at first increased and later much diminished or absent. With the disturbance of erythropoiesis, the formation of thrombocytes is inhibited.

AUTHORS' SUMMARY.

THE RELATION BETWEEN THE MITOCHONDRIA AND GLUCOSE-GLYCOGEN EQUILIBRIUM IN THE LIVER. E. M. HALL and E. M. MACKAY, *Am. J. Path.* 9:205, 1933.

Disturbances of the dextrose-glycogen equilibrium in the livers of rabbits have been produced by feeding large quantities of dried and fresh carrots followed by periods of fasting, by dextrose feeding to fasting animals and by injections of epinephrine into fasting animals. Excessive amounts of glycogen, as high as 13.1 per cent, were obtained in the animals fed dried carrots. Amounts ranging from 3.5 to 5.7 per cent were obtained in the animals fed fresh carrots and in those given dextrose. Injections of epinephrine produced mainly glycogenolysis. Marked changes in the mitochondria were found in the animals fed dried carrots. Instead of the usual short bacilliform rods, long filaments, coarse spherules and plump rods were found condensed about the nucleus and, to a lesser degree, about the cell membrane. Twelve hours of fasting in this group produced coarse spherules without a definite arrangement in the cytoplasm. Many of the spherules appeared to be semifluid. Administration of dextrose caused hypertrophy and enspherulation of mitochondria, with some tendency to paranuclear arrangement. We conclude that some relation exists between the mitochondria of the hepatic cell and the dextrose-glycogen equilibrium. Whether or not the chondriosomes act as catalysts, as they appear to do in the synthesis of fat within the hepatic cell, we are unable to say.

AUTHORS' SUMMARY.

PIGMENT DEPOSITS IN INTESTINAL MUSCLE IN RELATION TO DIET. E. NACHTNEBEL, *Am. J. Path.* 9:261, 1933.

A peculiar brown or buff pigmentation of the muscle coats of the intestinal tract has been observed in dogs. Some of the dogs had bile or Eck fistulas with or without anemia. Other dogs were in the anemia colony of the laboratory and had been continuously anemic from bleeding for various periods. Other dogs were normal. Age was not a factor. Microchemical reactions and staining properties of the pigment are given. On the basis of these tests one observes some similarity to the pigment observed in human disease (hemofuscin) and in old age. It is suggested that the pigment is not a definite entity but perhaps a pigment complex. The experiments indicate that it is of dietary origin due to some hepatic constituent which is absorbed. Observations on cases of anemia in human beings when large amounts of liver or liver fractions have been administered should prove of interest.

AUTHOR'S SUMMARY.

PASSAGE OF LIQUIDS FROM THE STOMACH TO THE INTESTINE. J. STEWART and W. N. BOLDYRÉFF, *Am. J. Physiol.* **102**:276, 1932.

From observations made principally on dogs with gastric fistulas, the following results are reported: Gastritis and duodenitis produce marked inhibition of gastric evacuation; even plain water was retained for from two to three times the normal period and was not exceeded in rapidity of evacuation by other fluids. No essential differences were observed in the evacuation of acids and alkalis of corresponding strengths. The emptying was prolonged by alcohol, mustard, pepper and other spices, certain bitter salts and peptone. The temperature, within a range from 2 to 50 C., had little effect on the emptying time. Duodenal regurgitation was found to be the most important factor in the neutralization of gastric acidity.

H. E. EGGERS.

EMPTYING OF THE GALL BLADDER. A. S. MARRAZZI, *Am. J. Physiol.* **102**:293, 1932.

In normal, fat-fed cats on which operation had not been performed the extent of the emptying of the gallbladder was studied by quantitative estimation of the bile evacuated. Additional studies were made of unanesthetized trained dogs by a new method of abdominal endoscopy, the endoscope being inserted through a trocar opening. The observation failed to show muscular contraction of the viscus while it was being emptied, nor was emptying produced by the administration of drugs stimulant to the smooth contraction of the muscles, nor by mechanical or electrical stimulation.

H. E. EGGERS.

MECHANISM OF ACTION OF PARATHYROID HORMONE. D. I. THOMSON and L. I. PUGSLEY, *Am. J. Physiol.* **102**:350, 1932.

It was found that the increase of serum calcium in dogs after the injection of parathyroid hormone is not necessarily associated with a decrease of total inorganic phosphate in the serum. When that is increased by the administration of dextrose and insulin, it causes only a slight increase of the calcium. The rate of disappearance from the blood stream of injected calcium does not appear to be affected by the simultaneous injection of the hormone, nor is the subsequent action of the hormone in the raising serum calcium apparently modified by the injection of the calcium. Apparently the hormone does not act by increasing the solvent action of the plasma for the calcium compounds of bone; the authors suggest that its effect may be stimulation of the osteoclastic process of bone.

H. E. EGGERS.

A PHYSIOLOGICALLY ACTIVE SUBSTANCE APPEARING DURING ANAPHYLACTIC SHOCK. C. A. DRAGSTEDT and E. GEBAUER-FUELNÉGG, *Am. J. Physiol.* **102**:512 and 520, 1932.

In these two articles the authors report that in the majority of cases of severe or fatal anaphylactic shock in dogs there appears, in the supradiaphragmatic vena cava and in the thoracic duct, a substance or substances which have the property of stimulating smooth muscle; the substance disappears rapidly, as the blood circulates, and only rarely can it be detected in the blood from the femoral vein. A series of tests of the substance, reported in the second paper, led to its identification in all probability as histamine.

H. E. EGGERS.

THE EFFECTS OF OVERDOSAGE OF IRRADIATED ERGOSTEROL. J. H. JONES and G. M. ROBSON, *Am. J. Physiol.* **103**:338, 1933.

Rats of from 68 to 138 days of age were fed an excess of viosterol sufficient to cause death in periods of from six to eight weeks. Examination of the femora showed marked degenerative changes, with greatly increased porosity due to the

removal of both the organic and the inorganic matrix, apparently by increased osteoclastic activity. There was a relative decrease of ash, which was apparently the result of the subsequent growth of osteoid tissue after the absorption of the bony matrix. The administration of large but nontoxic doses of viosterol to young rats on a diet low in calcium did not produce to any degree changes in the absolute amount of ash. Relatively the amount of ash was increased over that of rats that had been given the same basal diet without supplement, but the cause of the difference was greater development of osteoid tissue in the latter animals. The vitamin D under these circumstances would appear to restrain the overgrowth of osteoid tissue, failure to calcify being here due to insufficient calcium in the diet. In the animals receiving the vitamin D, the amount of blood calcium remained about normal, but in those which were given the basal diet alone it fell below 7 mg. per hundred cubic centimeters.

H. E. EGGERS.

PEPTIC ULCERS (GASTRIC, PYLORIC AND DUODENAL) IN GUINEA-PIGS. DAVID T. SMITH and M. McCONKEY, *Arch. Int. Med.* **51**:413, 1933.

Routine necropsies on 1,000 guinea-pigs maintained on our stock diet failed to show a single spontaneous peptic ulcer. Of 75 guinea-pigs fed diets deficient in vitamin C, in 20, or approximately 26 per cent, peptic ulcers developed which were similar in location and in gross and microscopic appearances to those observed in man. Of 80 guinea-pigs fed corresponding basic diets supplemented by vitamin C, in only 1 did peptic ulcer develop. Diets deficient in vitamins A, B and D did not cause peptic ulcers if the supply of vitamin C was adequate. Mechanical injury to the mucosa of the duodenum in guinea-pigs fed an adequate diet was followed by rapid and complete healing, while similar injury to guinea-pigs fed a diet deficient in vitamin C resulted in the formation of peptic ulcers. Peptic ulcer in the guinea-pig is apparently caused by a partial but prolonged deficiency of vitamin C.

AUTHORS' SUMMARY.

EXPERIMENTAL PYLOROSPASM AND GASTRIC RETENTION IN RATS. F. HOELZEL and E. DA COSTA, *J. Exper. Med.* **57**:597, 1933.

A method was found whereby the development of gastric retention could be studied in intact animals without the necessity of recourse to the use of x-rays. Gastric retention was found to develop as a result of the restriction of protein in seven of ten rats studied. Such retention could again be cleared up by protein realimentation or by allowing the animals free choice of protein, fat and carbohydrate. A diet high in protein following periods of undernutrition or prolonged restriction of protein usually gave rise to transient gastric retention. Diets with a solution of 25 per cent or more of alcohol added promptly gave rise to gastric retention in rats even when the protein content of the diet was adequate. Evidence is given indicating that the gastric retention which occurred in this study involved more or less pylorospasm, and possible influence of mechanical and chemical irritation and of the changes in the gastric mucin and in the flow of the bile on the development of pylorospasm are discussed. Spira's theory that fat in the diet gives rise to pylorospasm and ulceration is not supported by the results of the experiments.

AUTHORS' SUMMARY.

FACTORS IN THE HUMAN LIVER PRODUCING HEMOGLOBIN. G. H. WHIPPLE and F. S. ROBSCHT-ROBBINS, *J. Exper. Med.* **57**:637, 653 and 671, 1933.

The factors in the human liver which produce hemoglobin were estimated by feeding human liver to standardized anemic dogs under various conditions. It was found that acute infections reduce somewhat the hemoglobin-producing factors in the human liver; in arteriosclerosis, passive congestion, amyloid and fatty degeneration, carcinoma and cirrhosis with severe injury to the cells of the liver the

factors may be reduced. In untreated patients with pernicious anemia the factors producing hemoglobin may be increased in the liver; this is also true of aplastic anemia and secondary anemia due to destruction of the blood within the body.

THE LYMPHATIC PARTICIPATION IN HUMAN CUTANEOUS PHENOMENA. S. S. HUDACK and P. D. McMASTER, *J. Exper. Med.* **57**:751, 1933.

A technic is described for the demonstration of lymphatic capillaries in living skin and for their study. By means of vital dyes injected intradermally the vessels can be rendered plainly visible. They form an extraordinarily abundant anastomotic web. The least scratch, one which does not penetrate through the epidermis, gives rise to such conditions that lymphatic absorption readily takes place from the abraded surface; and so close-meshed is the lymphatic web that an intradermal injection with even the finest hypodermic needle tears some of the constituent vessels open, with the result that they undergo direct injection. In many persons much of the fluid introduced at an ordinary intradermal injection, like that made in the clinic, spreads through the superficial lymphatic network, whereas in others it tends to enter the deeper lymphatics at once, the difference being due to merely physical factors determined by the texture of the skin. Normal flow along the lymphatics of the skin is rapid even when the body is at rest, dye introduced into the skin of the resting forearm reaching the axilla within a few minutes. The observations make plain the fact that every intradermal injection is an intralymphatic one, often preponderantly such, while, furthermore, every local injection into the skin becomes within a few minutes a general one, so rapidly is the introduced material transported to the blood. The normal permeability of the lymphatics of the skin of man is approximately the same as that of the mouse. Tests indicate that in both instances the lymphatic wall behaves like a semi-permeable membrane. The permeability of the human lymphatic wall, like that of the mouse, is subject to rapid and great changes. A stroke on the skin with a blunt instrument to produce a wheal causes the lymphatic capillaries to become so permeable temporarily that dyes pass through their walls as if practically no barrier existed, instead of being held back for a greater or lesser period. Slight inflammation due to heat, ultraviolet rays or bacterial products has a similar effect. So, too, has histamine. When fluid pours rapidly into the tissue from the blood, as when a wheal is formed, the lymphatics are compressed, and their efficiency as drainage channels is interfered with. These facts are briefly discussed as to their bearing on cutaneous phenomena in general. The lymphatics cannot be disregarded in considering such phenomena, in which it is plain that they have a large share.

AUTHORS' SUMMARY.

MODERN TESTS OF LIVER EFFICIENCY APPLIED TO EXPERIMENTAL SHALE OIL LIVER NECROSIS. CYRIL POLSON, *Brit. J. Exper. Path.* **14**:24, 1933.

The following modern tests of the efficiency of the liver were applied to rabbits that had acute necrosis of the liver due to the administration of shale oil: the phenoltetrachlorophthalein test, the rose bengal test, the van den Bergh reaction and the levulose and galactose tolerance tests; the urea and amino-acid concentration of the blood was also determined. The development of an opalescence of the serum during the experiment precluded examination of the rose bengal test and limited observation of the phenoltetrachlorophthalein test. The results obtained with the latter prior to experiment showed that it was unlikely to be a reliable test. Coincident renal dysfunction was responsible in some measure for the increase in the urea concentration of the blood, and prevented an estimation of the severity of the dysfunction of the liver. A high concentration of amino-acid in the blood indicated gross damage to the liver, but it was observed only as a terminal phenomenon. The results of the levulose tolerance test were equivocal, and it was not until the fourth day that unqualified positive results were obtained. A positive result was invariably associated with gross damage to the liver, but severe damage

was present in a rabbit that gave a negative reaction on the third day. The galactose tolerance test was negative in two rabbits that had necrosis of the liver, but the lesion was invariably present when the test was positive. Damage to the liver was clearly indicated by this test, even on the second day of experiment in three of the five rabbits. Of the seven tests examined, this one is most likely to give a reliable indication of the presence of damage to the liver, and is probably able to detect damage of less severity than that which produced positive results in the other tests.

AUTHOR'S SUMMARY.

THE FAILURE OF PROLONGED ADMINISTRATION OF IRON TO CAUSE HAEMOCHROMATOSIS. CYRIL POLSON, *Brit. J. Exper. Path.* **14**:73, 1933.

The iron content of the livers of thirty-six adult rabbits was maintained at a high level for from one to four years. The terminal level in ten rabbits under experiment for from three to four years ranged from 3.42 to 7.67, and averaged 5.19 per cent dry weight. Cirrhosis of the liver and pancreatic damage were absent from all. It is therefore shown that excess of iron in the body over long periods caused neither cirrhosis of the liver nor hemochromatosis in rabbits, and it is unlikely that excess of iron is responsible for the hepatic and pancreatic lesions of human hemochromatosis.

AUTHOR'S SUMMARY.

MARROW ACTIVITY. A. E. BOYCOTT and C. L. OAKLEY, *J. Path. & Bact.* **36**:205, 1933.

Transfusion reduces the number of reticulocytes in the circulating blood; living in atmospheres with an excess of oxygen does the same. There is an intimate inverse relationship between the concentration of hemoglobin and the proportion of reticulocytes in the blood. Neither the persistent polycythemia resulting from repeated transfusions nor living in air rich in oxygen leads to the complete disappearance of reticulocytes from the blood. Rats do not become substantially anemic after living in air containing 65 per cent of oxygen.

AUTHORS' SUMMARY.

INFLUENCE OF SEXUAL HORMONES ON THE NUMBER OF BLOOD PLATELETS. GEORG BANKOW, *Beitr. z. path. Anat. u. z. allg. Path.* **88**:113, 1932.

The thrombocyte count in normal white rats varies between 180,000 and 220,000 per cubic millimeter. It is decreased during fasting and is highest four hours after feeding. The number of the thrombocytes is lower during the summer than during the winter. In both sexes, removal of the sexual glands or ligation of their blood vessels causes a marked decrease of the blood platelets which last two months. By subcutaneous injection of extracts of the sexual glands, the number of thrombocytes is markedly increased and reaches its maximum thirty-five days after injection. After this period the number decreases slowly and is again normal at the end of the second month.

C. ALEXANDER HELLWIG.

PHYSIOLOGY AND PATHOLOGY OF THE PALATINE TONSIL. HERMANN HOEPKE, *Beitr. z. path. Anat. u. z. allg. Path.* **88**:207, 1932.

In the normal tonsil, the centers of the lymph follicles are germinal centers, producing small lymphocytes from reticulum cells and lymphoblasts. In the chronically inflamed tonsil, the germinal centers are transformed into reactive centers. The formation of small lymphocytes decreases or ceases entirely. As a defense reaction against bacteria and toxins, only reticulum cells and macrophages are produced, and the reactive centers attain considerable size when the irritation is of long duration. The capsule is thickened and impedes the emigration of newly formed cells, which appear threadlike. The cells are carried by stagnating

lymph fluid to the periphery. There is a stagnation in the lymph and in the blood vessels, and there may be even a retrograde lymph flow, causing rupture of the lining epithelium of the tonsil.

C. ALEXANDER HELLWIG.

INFLUENCE OF FREEZING ON THE TESTIS OF THE GUINEA-PIG. T. J. ARJEW, Beitr. z. path. Anat. u. z. allg. Path. **88**:395, 1932.

Ethyl chloride sprayed on the testes of guinea-pigs produces degenerative and productive changes in the sex cells and in the interstitial tissue. In the periphery, the entire epithelial wall of the seminiferous tubules is destroyed. In the central portions of the gland, the spermia die first, then the spermatids, spermatocytes and the spermatogonia, in the order named. The Sertoli cells are highly resistant and may remain intact in the otherwise necrotic tubules. The interstitial tissue reacts against freezing temperature in the first stage by producing an exudate and by proliferation of cells. Hemorrhages are found in the tunica albuginea and in the interstitial tissue. During the reparative stage, many multinuclear giant cells are formed by the spermia and spermatids. The Sertoli elements do not undergo mitotic or amitotic cell division. The interstitial tissue finally replaces the necrotic seminiferous tubules by scar tissue.

C. ALEXANDER HELLWIG.

EFFECT OF ROENTGEN RAYS ON THE SPLEEN OF THE FROG AND SALAMANDER. P. W. SSIPOWSKY, Beitr. z. path. Anat. u. z. allg. Path. **88**:413, 1932.

The intensity of the lesions in the spleen following irradiation corresponds to the dosage of the x-rays. It is also dependent on the intensity of the rays. Irradiation produces necrobiosis of the lymphocytes and hypertrophy of the reticulum cells; there are pyknosis, karyorrhexis and finally complete fragmentation of the erythrocytes. The number of pigmented cells and hemocytoblasts is increased. Owing to the destruction of erythrocytes, the reticulum cells of the spleen and liver contain a great amount of iron.

C. ALEXANDER HELLWIG.

EFFECT OF THYROXINE ON YOUNG WHITE MICE. HANNA SCHULZE, Beitr. z. path. Anat. u. z. allg. Path. **90**:142, 1932.

White mice received daily subcutaneous injections of thyroxine from the day of birth to the time of sexual maturity. The dosage was increased progressively and varied in different animals. Mice appear to be highly resistant to the acute toxic action of thyroxine. Litters were reduced to four, two of which were kept as controls. The control animals received daily injections of sterile physiologic solution of sodium chloride. The animals treated with thyroxine were stunted, as compared with their litter-mate controls, but their development was more rapid, as determined by the time of appearance and the rate of growth of the incisor teeth. Marked changes were noted in the hair and skin of the thyroxinized animals. Their hair became wooly, and much of it was lost. The bald patches of the skin became ulcerated. The eyelids became inflamed and finally closed. Both male and female animals treated with thyroxine were sterile. Precocious union of the epiphysis and diaphysis of the bones led to dwarfing of the skeleton. The thyroid and thymus were smaller than those of control litter-mates. The heart was hypertrophied. The other internal organs revealed only inconstant changes. Microscopic examination of the testes and ovaries is not recorded.

O. T. SCHULTZ.

EXPERIMENTAL CHANGES IN LYMPHOID FOLLICLES. E. JECKELN, Beitr. z. path. Anat. u. z. allg. Path. **90**:244, 1932.

The animals used in Jeckeln's experiments were chiefly guinea-pigs. The experimental procedures consisted in the subcutaneous or intraperitoneal injection of diphtheria toxin, the subcutaneous injection of killed cocci (pneumococcus or

staphylococcus vaccine) and the oral administration of sodium fluoride. The author is convinced that the state of the lymphoid tissues may vary in animals of the same species and age kept under identical conditions. To overcome this factor, in one series of experiments small pieces of the spleen were removed before the injection of diphtheria toxin and other pieces at various times after injection. The results of the experiments have a bearing on the controversy over whether the centers of the lymphoid follicles are true germinal centers in the sense of Flemming or are secondary reaction centers in the sense of many recent writers. The earliest change noted by Jeckeln, following mild stimuli, was a state of lymphatic hyperplasia, characterized by transformation of the center of the follicle into a germinal center, in which there occurred a production of lymphocytes from lymphoblasts. More severe or more prolonged action led to nuclear fragmentation, which was most marked in the center. This phenomenon was followed by transformation of the follicle into a reaction follicle, characterized by proliferation of the reticulo-endothelial cells of the follicle.

O. T. SCHULTZ.

EXPERIMENTAL MALFORMATIONS OF THE CHICK EMBRYO. V. PAPILIAN and A. NANA, *Virchows Arch. f. path. Anat.* **287**:5, 1932.

The authors gave a brief description and histologic study of maldevelopments of the brain and the heart of four chick embryos after centrifugation of the eggs for periods of from three to five minutes. The resulting maldevelopments are explained as due in part to inhibition of development and in part to tumor-like proliferation of the tissue.

O. T. SCHULTZ.

DIETARY PROTECTION AGAINST NECROSIS OF THE LIVER DUE TO ARSPHENAMINE. A. SCHRIFRIN, *Virchows Arch. f. path. Anat.* **287**:175, 1932.

One group of dogs was maintained on a diet high in carbohydrate, another on a diet high in fat and a third on a diet high in protein (meat). The animals received intravenously from 0.03 to 0.04 Gm. of arsphenamine in alkaline solution per kilogram of body weight. Contrary to many statements in the literature, the diet high in carbohydrate did not protect the animals against focal necroses of the liver, as it was less efficacious in this respect than the diet high in protein. The diet high in fat rendered the animals susceptible to hepatic damage; it was found that the van den Bergh reaction was not a satisfactory index of the degree of damage. The damage is primarily entirely parenchymatous; the stroma reaction is secondary.

O. T. SCHULTZ.

PATHOLOGIC STATES ENCOUNTERED AMONG CHINESE. J. HEINE, *Virchows Arch. f. path. Anat.* **287**:203, 1932.

This article is a report of the kinds of pathologic lesions encountered in the examination of 1,064 specimens from the surgical operating room and from 106 necropsies. All the subjects were Chinese. The work was done in the pathologic institute of Hung Chi University in Shanghai. The author expresses the belief that variations in the frequency and the character of different diseases among the Chinese, as compared with western races, bear no relation to hereditary constitutional racial factors, but are probably due entirely to external factors.

O. T. SCHULTZ.

ERYTHROPOIESIS IN ENDEMIC GOITER. S. I. SCHERMANN, *Virchows Arch. f. path. Anat.* **287**:363, 1932.

In 160 patients with endemic goiter in the Mari Territory of central Russia, reticulocyte counts were made by Schilling's method. The author believes that this is the best method of determining the erythropoietic function of the bone

marrow. In ninety-one patients a moderate increase in the reticulocytes was found. The finding of an increased erythropoietic activity of the bone marrow in hypofunction of the thyroid is contradictory to the common opinion that hypothyroidism exerts an inhibiting effect on the function of the bone marrow. It seems likely that the thyroid excretion does not exert any direct action on blood-forming organs.

W. SAPHIR.

Pathologic Anatomy

EXTENSIVE DECALCIFICATION OF THE BONES IN AN EIGHT YEAR OLD BOY.

A. J. ABELOFF, I. P. SOBEL and A. BERNHARD, *Am. J. Dis. Child.* **45**:105, 1933.

A case of unusual and extensive rarefaction of the bones is reported in an 8 year old boy. Specimens were removed from the distal femoral metaphyses. Sections of decalcified bone showed widening of the marrow spaces with rarefaction of the trabeculae. The marrow was for the most part of the ordinary fatty type, though in localized areas it was fairly rich in cells. A few of the marrow spaces were occupied by loose vascular granulation tissue, and the corresponding trabeculae were bordered by osteoclasts. However, there was not sufficient evidence to warrant a diagnosis of fibrous osteitis, the ratio of the calcium excreted in the urine to that eliminated in the feces being normal. The blood calcium was not elevated. Study of the calcium and phosphorus metabolism revealed subnormal retention.

RALPH FULLER.

INJURIES PRODUCED BY CONTACT WITH ELECTRIC CIRCUITS. ORTHELLO R.

LANGWORTHY and WILLIAM B. KOUWENHOVER, *Am. J. Hyg.* **16**:625, 1932.

Rats were used in the study of injuries caused by contact with electric currents. Paralysis of the posterior parts of the body and of the extremities occurred frequently following shocks with high voltage alternating current. Postmortem examinations of paralyzed rats usually revealed the rupture of a small artery in the posteromedial septum of the cord, less frequently in the ventrolateral columns. The spinal cord possessed a characteristic appearance; in the upper thoracic and cervical regions the posterior columns appeared lavender, cross-sections revealing a large hemorrhage. Hemorrhage in the subarachnoid space was observed in a number of animals. On microscopic examination small hemorrhages were found in the substance of the brain, most commonly in the brain stem. Rather commonly there was rupture of the arteries of the choroid plexus with hemorrhage in the cerebral ventricles. Damage to nerve cells was more apparent after injury with continuous current. Sections of brain stained with thionine and hematoxylin and eosin showed various degrees of injury. In the cells most severely injured the nuclei were shrunken and stained an intense blue, so that the skeins of chromatin and the nucleoli could not be distinguished. In cells less severely injured the nucleoli were swollen and the nuclei shrunken and stained darkly. The injury seemed selective in that abnormal cells could be found among groups of comparatively normal cells and in that the Purkinje cells seemed most markedly injured.

RALPH FULLER.

A MICROSCOPIC STUDY OF THE TISSUES OF THE ALBINO RAT FOLLOWING THE INGESTION OF ALUMINUM SALTS. ERNEST SCOTT and MARY K. HELZ, *Am. J. Hyg.* **16**:865, 1932.

The conclusions reached in this study are based on the findings in eighty test and twenty-two control white rats which had received varying amounts of aluminum salts up to 3.6 per cent of their food by weight. The protracted ingestion of aluminum salts in concentrations as high as 3.6 per cent had no deleterious effect on the growth, reproduction or blood. The livers examined contained a normal

amount of iron. There was no gross or microscopic evidence in the organs examined of a pathologic condition which could be attributed to the ingestion of aluminum salts. Autolytic changes in the stomach and intestine occurred only when these organs contained partly digested food. Animals which had fasted for twenty-four hours before they were killed seldom showed this condition. We therefore found no lesions in the gastro-intestinal tract which could be attributed to the presence of aluminum.

AUTHORS' SUMMARY.

NOURISHMENT OF THE MYOCARDIUM THROUGH THEBESIAN VESSELS. S. BELLET, B. A. GOULEY and T. M. McMILLAN, *Arch. Int. Med.* **51**:112, 1933.

The heart of a 16 year old boy is described in which an unusual degree of tuberculous fibrocaseous infiltration had destroyed the coronary arteries and the large surface veins. A system of sinusoids (thebesian vessels), many of which were dilated and some of which had thickened walls, connected the endocardium with the remaining intramural veins and furnished the only means of myocardial nourishment. The unusual pathologic cause of the obliteration of the coronary circulation (both arteries and veins) prevents a direct and exact comparison of the circulatory features of the heart described with those seen in double coronary occlusion of the more chronic types.

AUTHORS' SUMMARY.

NECROSIS OF THE SPINAL CORD PRODUCED BY ELECTRICAL INJURIES O. R. LANGWORTHY, *Bull. Johns Hopkins Hosp.* **51**:210, 1932.

Anesthetized rats were subjected to alternating electric circuits at different potentials (from 18 to 1,000 volts), the contacts being made with the dorsal surface of the head and of the tail. Complete paralysis of the posterior portion of the body with incontinence developed in many of the animals. It is thought that the injury was caused by the direct action of the current on the spinal cord. The lesion, in general, remained confined to the posterior columns, although sometimes the whole cord became necrotic. The cavity contained relatively few red blood cells but many fat droplets and some amorphous debris. Similar cavities develop in the spinal cord of man as the effect of concussion after injuries suffered in war. The posterior columns appear to be particularly susceptible to injury, while the gray matter of the cord offers considerable resistance to the spread of the lesion.

AUTHOR'S SUMMARY.

ACUTE PNEUMOCOCCAL NEPHRITIS. S. S. BLACKMAN and G. RAKE, *Bull. Johns Hopkins Hosp.* **51**:217, 1932.

Acute nephritis was found in 9.4 per cent of ninety-five cases of pneumococcic infections (lobar pneumonia, organizing pneumonia, empyema, pericarditis, otitis media and meningitis). The microscopic character of the nephritis corresponds to that produced in rabbits by the intravenous injection of pneumococcus toxin. The kidneys of young children seem especially susceptible to injury by pneumococcus toxin. Outspoken examples of acute nephritis were found only in infants with pneumococcic infections, usually of long duration, other than pneumonia alone. The condition was not present in adults who had similar chronic pneumococcic infections. Slight or moderate changes, besides cloudy swelling, have been found in 76.8 per cent of the kidneys examined. This damage of slight degree, occurring in the kidneys of adults and children, differs only in extent from that found diffusely in the kidneys of infants with distinct acute nephritis.

AUTHORS' SUMMARY.

THE EXTRACARDIAC ANASTOMOSES OF THE CORONARY ARTERIES. C. L. HUDSON, A. R. MORITZ and J. T. WEARN, *J. Exper. Med.* **56**:919, 1932.

Widespread anastomoses of the auricular branches and the coronary branches to the pericardial fat with the pericardiacophrenic branches of the internal mammary

arteries and the anterior mediastinal, pericardial, bronchial, superior and inferior phrenic, intercostal and esophageal branches of the aorta have been described. The most extensive anastomoses between the cardiac and the extracardiac vessels are around the ostia of the pulmonary veins. It was possible not only to demonstrate the passage of an injected mass from the coronary arteries into the vessels of surrounding structures, but to show that the material passed into vessels in the heart from the thoracic branches of the aorta. This rich potential extracardiac coronary collateral circulation is probably of significance in compensating for sclerosis of the large trunks of the coronary arteries. [Four hearts with pericardial adhesions into which injections were made by way of the coronary arteries are described by A. R. Moritz, C. L. Hudson and E. S. Orgain (*J. Exper. Med.* 56:927, 1932).]

AUTHORS' SUMMARY.

HEPATIC LESIONS IN ECLAMPSIA AND FROM RAISING INTRA-ABDOMINAL PRESSURE. G. W. THEOBALD, *J. Path. & Bact.* 35:843, 1932.

Severe degenerative and necrotic changes in the livers of dogs, sometimes associated with hemorrhagic necroses in the periphery of the lobules, may be caused by frequently raising the intra-abdominal pressure to between 80 and 100 cm. of saline solution for thirty seconds or longer. It is probable that the hepatic lesions associated with eclampsia and the coincident hemorrhages in the other organs of the body are more often the result than the cause of the convulsions which may be initiated by the onset of labor. It is possible to account for the degenerative changes in the liver associated with hyperemesis gravidarum in a similar manner. The damage to the liver caused during the second stage of obstructed labor, and possibly in many cases of normal labor, is probably an important factor in lowering the resistance of the body to puerperal infection.

AUTHOR'S SUMMARY.

A CASE ILLUSTRATING THE EFFECTS OF PROLONGED ACTION OF RADIUM. J. M. ROSS, *J. Path. & Bact.* 35:899, 1932.

A case is described in which a radium needle with a wall thickness of 0.5 mm. of platinum, containing 2 mg. of radium in the form of radium sulphate, had been embedded in the interventricular septum of the heart for three years. The pericardial cavity was almost obliterated by firm adhesions. A zone of necrotic heart muscle extended around the needle for a radius of $1\frac{1}{2}$ inches (3.7 cm.). The changes in the heart muscle were apparently due to alterations in its blood vessels. The spleen and the lymphadenoid tissue showed: proliferation and activity of macrophages, loss of the follicular structure of the lymphoid tissue, disappearance of lymphocytes, and replacement of lymphocytes by plasma cells. It is suggested that these changes are a result of vascular disturbances induced directly or indirectly by irradiation. The blood picture after one year's irradiation showed relative and absolute lymphopenia. It is suggested that this is due to deficient production and to metamorphosis of lymphocytes into plasma cells. The liver was found to contain a malignant hemangio-endothelioma in a zone immediately subjacent to the needle. Metastatic growth was present in the lungs and bone marrow. The origin of the tumor can be traced to the endothelial lining of the branches of the portal vein. It is suggested that the growth was caused indirectly by the action of prolonged irradiation on the vessels near the surface of the liver. Finally, therefore, the case affords additional evidence that the necrotizing and carcinogenic action of gamma radiation results from the susceptibility of the vascular system to irradiation.

AUTHOR'S SUMMARY.

SCLEROPIGMENTARY FORMATIONS IN THE SPLEEN. D. S. ELEFThERIOU, *Ann. d'anat. path.* 9:1, 1932.

In a 40 year old woman who died of chronic nephritis and uremia, the spleen was atrophic, weighing only 70 Gm., but showed many areas of incrustation by

brownish-red iron pigment, with sclerosis and calcification, characteristic of so-called mycotic splenomegaly. Microscopic examination revealed a perivascular location of these areas, as well as a proliferating vascular stroma in the vicinity. The author believes the condition to be primarily vascular, resulting in successive hemorrhages. Whether the sclerosis represents a primary vascular injury or secondary organization could not be determined. The peculiar mycelium-like, fibrillar, reticular and spheroidal structures are considered to be degenerative, not mycotic. The chief points of view expressed in the literature on the subject are reviewed.

PERRY J. MELNICK.

A CASE OF "CATARRHAL" JAUNDICE WITH BIOPSY. A. SCHRUMPF, *Ann. d'anat. path.* 9:17, 1932.

A 39 year old woman with catarrhal jaundice was operated on, on the eighth day of her illness, because of an incorrect diagnosis of cholelithiasis. A specimen of the liver was taken for biopsy. Microscopic study revealed a characteristic severe diffuse hepatitis, and not cholangitis. This supports the newer view held by Klemperer, Killian and Heyd, and Eppinger.

PERRY J. MELNICK.

PROLIFERATING THROMBOPOIETIC ENDOVASCULITIS. FOLKE HENSCHEN, *Ann. d'anat. path.* 9:113, 1932.

Henschen disagrees with the conception that so-called intravascular endothelioma is a tumor. From a study of many such lesions in hemorrhoids, urethral polyps and other conditions, he concludes that the endothelial proliferation results from a toxic or inflammatory stimulus. There is an associated thrombosis, but the latter can be followed through various stages and is seen to be secondary. Hence he proposes the name proliferating thrombopoietic endovasculitis.

PERRY J. MELNICK.

MYCOTIC SPLENOMEGALY. N. HORTOLOMEI, N. BALAN and T. BURGHELE, *Ann. d'anat. path.* 9:145, 1932.

This critical review covers the subject thoroughly, and there is an extensive bibliography. From the heterogeneous group of conditions which went under the name of Banti's syndrome, namely, splenomegaly, anemia, hemorrhages, ascites and cirrhosis, Gamna of Italy, in 1922, separated an entity in which the spleen presents tobacco-colored nodules of iron pigment. (A case of this type had first been described by Gandy in 1905; hence the name Gandy-Gamna nodules.) Soon this condition was recognized in many other countries. It was differentiated in Algeria from kala-azar and in Egypt from bilharziasis. At first various organisms were thought to be etiologically concerned, but when peculiar mycelium-like structures were discovered in the lesions, a mycotic origin of the disease was accepted. Cultures and inoculation of animals have, however, given negative results. The portals of entry of the fungi are considered to be ulcerations of the skin or lesions of the gastro-intestinal tract which are frequently found associated. However, the fungi have also been considered to be secondary invaders associated with other primary conditions, such as Hodgkin's disease and leukemia. Furthermore, the mycotic origin of this condition has been strongly contested, the mycelium-like structures being considered artefacts. The authors present a case of their own.

PERRY J. MELNICK.

THE BONE MARROW IN CIRRHOSIS OF THE LIVER. JEAN ROSSIER, *Ann. d'anat. path.* 9:245, 1932.

The author studied the bone marrow in thirty-nine cases of Laënnec's cirrhosis and in nine cases of cirrhosis of other types. In the majority (90 per cent) there was a peculiar hyperplasia of the bone marrow, namely, a dissociated reaction.

There was marked myeloblastic and erythroblastic proliferation, but a diminution of megakaryocytes and thrombocytopoiesis. The close resemblance of the picture to that of the bone marrow in pernicious anemia brings up the possibility of a primary or secondary toxic influence, perhaps associated with the liver. Other conditions may have an influence, such as repeated hemorrhages, hemorrhagic diathesis, various infectious conditions, for instance, chronic gastritis and biliary and hepatic infections, and also endocrine dysfunction. The last mentioned condition was especially studied by Barrelet with the same material; he found testicular atrophy and a decrease in the weight of the thyroid gland.

PERRY J. MELNICK.

CALCIFIED ECHINOCOCCUS CYSTS. PEDRO JAUREGUI and JOSÉ L. MONSERRAT, *Ann. d'anat. path.* 9:345, 1932.

Four cases of calcified echinococcus cysts were studied in detail with reference to the perilydatid membrane, the process of calcification and histologic demonstration of calcium. The various theories of calcification are discussed as applied to the calcification of these cysts. The various methods for histologic demonstration of calcium are given, as well as a new method devised by Monserrat. Three photomicrographs show the crystalline structure of the calcium as demonstrated by Monserrat's method.

PERRY J. MELNICK.

THE GLANDS OF INTERNAL SECRETION IN CIRRHOSIS OF THE LIVER. J. BARRELET, *Ann. d'anat. path.* 9:391, 1932.

The same material that was used by Rossier (*Ann. d'anat. path.* 9:245, 1932) was studied by Barrelet with reference to the glands of internal secretion. The most important finding was atrophy of the testicles with proliferation of the interstitial cells in most cases. In women there was atrophy of the ovaries. The thyroid gland was markedly atrophic and was decreased in weight, with a decrease in the amount and a change in the character of the colloid. The hypophysis at times showed an increase in basophilic cells; the suprarenals, a decrease in lipoid, and the pancreas, an increase in connective tissue and occasional fibrosis of the islands.

PERRY J. MELNICK.

A CASE OF PSEUDOMYXOMA OF THE HEART. J. MONTPELLIER and R. RAYMOND, *Ann. d'anat. path.* 9:511, 1932.

In a case of far-advanced pulmonary tuberculosis there was found attached to the endocardium of the left auricle a nut-sized mass which had the histologic structure of pseudomyxomatous tissue. The mass was interpreted to be not a tumor but a mural thrombus which was undergoing an abortive organization.

PERRY J. MELNICK.

ORIGIN OF THE SENILE PLAQUES OF THE CEREBRAL CORTEX. L. MARCHAND, *Ann. d'anat. path.* 9:569, 1932.

Marchand made histologic studies in ten cases of senile cortical plaques, using the Bielschowsky, Hortega, Cajal and Weigert-Pal and other methods. The plaques never reach more than 80 microns in diameter and are almost confined to the gray matter. They consist of localized degenerative changes depending on vascular changes, especially arteriolosclerosis. The degenerative changes consist of an alteration in the fibrillar network of the gray matter, which becomes argyrophil; they result in the formation of lipoid droplets. Fibrillar and protoplasmic glia encroach on the plaque. The central portion is composed of an amorphous material resulting from the products of degeneration of various sorts of fibrils. In the pyramidal layer rodlike and granular particles are formed from the debris of the axis cylinders or neurofibrils. In the molecular layer giant astrocytes are found. There is no inflammatory reaction in the periphery of the plaques.

PERRY J. MELNICK.

PIGMENTARY CIRRHOSIS AND BRONZE DIABETES. MARCEL LABBÉ and MIRCEA PETRESCO, *Ann. d'anat. path.* 9:697, 1932.

The authors present seven cases of pigmentary cirrhosis of the liver, of which five were classic cases of bronze diabetes. The constant factor in all was the cirrhosis and hemosiderosis of the liver. The pancreas also presented variable degrees of cirrhosis and hemosiderosis. The islands of Langerhans were absent in six cases. The spleen was generally only slightly or not at all affected. The lymph nodes were not involved except for those in relation to the liver and pancreas, which were converted into veritable "iron mines." The endocrine glands showed minor changes. The other organs were not affected. The various aspects of the disease are discussed.

PERRY J. MELNICK.

EXTRAGLANDULAR LESIONS OF LYMPHOGRANULOMATOSIS. PAUL FOULON, *Ann. d'anat. path.* 9:725, 1932.

The author discusses the lésions of Hodgkin's disease of the liver, lung, spleen, bones and gastro-intestinal tract. In general, two modes of spread of the lesion are evident. The first is a circumscribed nodular form secondary to a lymphangitic metastatic process. The second is characterized by a diffuse activation of the potential reticulo-endothelial elements of an organ.

PERRY J. MELNICK.

ALTERATIONS OF BLOOD VESSELS IN TUBERCULOUS CAVITIES. M. KASPER, *Beitr. z. Klin. d. Tuberk.* 80:537, 1932.

The protruding ridges in cavities frequently do not contain any vessels. The wall of the cavity is usually composed of three layers: first, a necrotic inner layer; second, a layer of granulation tissue, and third, a layer of connective tissue. The vascular alterations are different in the various layers. Within the cirrhotic tissue the adventitia is thickened. There is usually a cellular infiltration, most marked in the adventitial layer and least marked in the intima. In the granulation tissue the adventitia is more or less destroyed; the media contains vessels and is infiltrated, and it may be hypertrophic or atrophic. The thickened intima contains capillaries. The lumen becomes narrower and is usually eccentrically located. In general the alterations of the blood vessel walls depend on the nature of the tuberculous process. In the necrotic layer, destructive changes predominate. The media and even the hypertrophied intima are destroyed. The lumen is almost always obliterated before destruction occurs. Thrombosis is rare. Tubercle bacilli have never been found in the vessel walls, and caseation is rare.

MAX PINNER.

CHANGES IN THE OPTIC NERVE IN POSTVACCINAL ENCEPHALOMYELITIS. F. V. HERRENSCHWAND, *Beitr. z. path. Anat. u. z. allg. Path.* 87:161, 1931.

In one case there was perineuritis, the infection apparently descending from the meninges. The inner layers of the dura showed perivascular lymphocytic infiltration and marked proliferation of fibrocytes with extension into the nerve. The second case presented an acute retrobulbar neuritis with changes similar to those found in the white matter of the brain. Numerous focal proliferations of glia, especially of Hortega microglia, were arranged perivascularly, especially about the central retinal vein at its point of entry into the optic nerve. Perifocal edema and marked degeneration of sheaths and axis cylinders were present. The meninges of the optic nerve were free. The similarity to the changes in myelitis, multiple sclerosis and epidemic encephalitis, except for the perivenous glia proliferation, is emphasized.

W. S. BOIKAN.

INTESTINAL CHANGES IN PELLAGRA. W. CELEN, *Beitr. z. path. Anat. u. z. allg. Path.* 87:488, 1931.

Celen's investigations of the gastro-intestinal tract in pellagra revealed severe enterocolitis of the small, and especially of the large, intestine which corresponded

to the microscopic observations of marked atrophy, superficial focal necrosis, dense infiltration and cystic glandular changes. These changes are considered the result of pellagra and not primary in the pathogenesis of the disease, which is essentially nutritive in origin.

W. S. BOIKAN.

RELATION OF SPECIFIC GRANULATIONS OF CELLS OF ISLANDS OF LANGERHANS TO DISTURBANCES IN CARBOHYDRATE METABOLISM. H. HINTEREGGER, *Beitr. z. path. Anat. u. z. allg. Path.* **87**:535, 1931.

In addition to the A and B cells described by Lane in the islands of Langerhans, the author describes a transitional cell between these two types. He considers the B cells the insulin-producing cells and believes that the A cells, the function of which is not known, may be precursors of the B cells, through the transitional cell stage. The transitional cells are not found in normal islands but in those which show a disturbed relationship of A and B cells. In the pancreas of pregnant guinea-pigs, there is a diminution of B cells with an increase of A cells. Animals given injections of insulin for a prolonged period show similar changes. Scorbutic animals show islands composed almost exclusively of B cells. In starved animals the islands either disappear or have an increased proportion of A cells.

W. S. BOIKAN.

TOXIC ENDOCARDITIS. H. WILLER, *Centralbl. f. allg. Path. u. path. Anat.* **56**: 1, 1932.

Willer raises the question of whether a pure toxic form of endocarditis can occur, concludes that this diagnosis may be accepted in the absence of bacterial infection and then offers an interesting observation in support of his ideas. The patient whom he observed was a 30 year old rachitic dwarf in whom, during her first pregnancy, in 1927, some symptoms of eclampsia developed. When he first observed her in 1931 she was five months pregnant, and had a blood pressure of 110 systolic and 70 diastolic and normal urine. When she was eight months pregnant eclampsia developed. She had a blood pressure of 180 systolic and 100 diastolic, many casts in the urine and large quantities of albumin. The patient died thirty hours after a cesarean section. Necropsy revealed: edema of the brain; thrombotic verrucous masses on the auricular surface of the mitral valve leaflets, surrounded by hemorrhagic regions; recent bronchopneumonia and hypostatic hyperemia of the lower lobes of both lungs; typical eclamptic changes in the liver, and acute degenerative as well as old fibrotic changes of the kidneys. Sterile cultures were obtained from the blood, spleen and heart valve leaflets. The only change in the body that cast doubt on the purely toxic character of the cardiac lesion was the bronchopneumonia. The author believes that endocarditis follows croupous pneumonia rather than bronchopneumonia. He also stresses the fact that the cardiac lesion in this case was older than the pneumonia. He concludes, therefore, that he dealt with a pure toxic endocarditis on an eclamptic-uremic basis.

GEORGE RUKSTINAT.

GASTRIC MUCOSA IN ULCER AND IN CARCINOMA. HORST PUCHERT, *Virchows Arch. f. path. Anat.* **280**:385, 1931.

Sixty resected stomachs with carcinoma or ulcer as well as a series of normal stomachs from autopsies were carefully studied histologically. In peptic ulcer of the stomach and duodenum there is an associated gastritis of a subacute type, verging on the chronic; this is not found in the fundus but is confined to the antrum. There is an increase in the size and number of the lymph follicles. There is very little epithelial metaplasia. In carcinoma there is a chronic pangastritis involving the entire mucous membrane. The lymph follicles are increased in number, but are small and show regressive changes. There is pronounced epithelial metaplasia. Bacteriologic examination in these cases gave negative results, leading to the conclusion that the toxic products of tissue necrosis are a factor in the production of the gastritis.

PERRY J. MELNICK.

SURFACE OVARIAN PREGNANCY AND ITS CLINICO-HISTOLOGIC DIAGNOSIS. GUSTAV GERSTEL, *Virchows Arch. f. path. Anat.* **280**:435, 1931.

The reported cases of ovarian pregnancy are reviewed. A case is reported which clinically appeared to be one of ruptured ectopic pregnancy. At operation the hemorrhage was found to come from one ovary. Microscopic examination revealed chorionic villi on the surface of a hemorrhagic mass which protruded from the ovary; these might have been easily overlooked. The possibility is considered that so-called idiopathic ovarian hemorrhages are really ovarian pregnancies which have not been recognized.

PERRY J. MELNICK.

MECHANISM AND SIGNIFICANCE OF THE CHANGES IN THE PULMONARY VESSELS IN INFLUENZAL PNEUMONIA. M. H. CORTEN, *Virchows Arch. f. path. Anat.* **280**:463, 1931.

In forty deaths from influenzal pneumonia in Hamburg during the winter of 1928 and 1929 the vascular changes in the lungs were found to be significant. In the early part of the epidemic the pneumonia was a hemorrhagic bronchopneumonia, later a serohemorrhagic lobar pneumonia, then a suppurative lobar pneumonia and finally an interstitial suppurative pneumonia. An apparently primary vascular injury was found to run a parallel course. At first there was necrosis restricted to the intima, with thrombosis and resulting hemorrhage. Later there was necrosis of the media; toward the end of the epidemic a suppurative arteritis developed and finally periarteritis, leading to an interstitial pneumonia. Similar vascular changes were observed in Berlin in 1930, and also during the pandemic of 1918.

PERRY J. MELNICK.

SO-CALLED PELIOSIS OF THE LIVER. W. GEISLER, *Virchows Arch. f. path. Anat.* **280**:565, 1931.

A review of the reported cases of so-called peliosis of the liver and two additional cases are presented. All except three doubtful cases were in tuberculous persons. The condition is a multiple telangiectasia of the central and sublobular veins of the liver and not multiple hemorrhages. It is occasionally associated with telangiectasia of the spleen. The etiologic factor is not considered to be tuberculotoxic, but a constitutional defect resulting in the angiectasis.

PERRY J. MELNICK.

CALCAREOUS CONCRETIONS OF THE SPLEEN. O. LUBARSCH, *Virchows Arch. f. path. Anat.* **286**:253, 1932.

The small calcified nodules sometimes seen in the spleen are usually phleboliths or calcified animal parasites. Lubarsch describes three spleens in which the nodules were situated in the malpighian bodies and were the result of an inflammatory reaction in the arteriole of the follicle.

O. T. SCHULTZ.

ACUTE PURULENT AORTITIS. O. AUERBACH, *Virchows Arch. f. path. Anat.* **286**:268, 1932.

In a man, aged 81, acute suppurative inflammation of the arch of the aorta was secondary to cystitis and pyelonephritis. The ulcerative defect of the intima was covered by mural thrombus. In a woman, aged 34, the lesion of the aorta was of longer duration and was secondary to ulcerative endocarditis of the aortic valve. The process may lead to rupture or aneurysm of the aorta and hence may be confused with syphilis. In their histopathologic changes, healing lesions of longer duration may simulate syphilitic aortitis.

O. T. SCHULTZ.

FREQUENCY OF ASSOCIATION OF CHRONIC VALVULAR ENDOCARDITIS WITH ARTHRITIS DEFORMANS. N. GRZIMEK, *Virchows Arch. f. path. Anat.* **286**: 286, 1932.

A probable rheumatic origin of arthritis deformans may be inferred if this disease reveals an unusually high frequency of association with a common stigma of rheumatic infection, such as chronic valvular endocarditis. Of 520 knee joints examined at necropsy in an unselected series of necropsies of persons aged from 16 to 89, 91 revealed changes that were considered characteristic of arthritis deformans. Of the latter group, 42.8 per cent revealed healed or recurring valvular endocarditis. The latter condition was noted in only 17.9 per cent of the necropsies in which the knee joint was free from arthritis deformans.

O. T. SCHULTZ.

CHANGES IN THE COLLAGENOUS FIBRILS IN RHEUMATIC INFECTION AND IN OTHER INFLAMMATORY PROCESSES. F. SCHNOSNIG, *Virchows Arch. f. path. Anat.* **286**:291, 1932.

The earliest and most striking tissue reaction in rheumatic fever is the change that Klinge and his associates have termed fibrinoid degeneration of the ground substance of connective tissue. In this process the collagenous fibrils retain their identity, but become separated from each other and can be impregnated with silver by a modified Bielschowsky method. The present contribution presents the results of a study, by this method, of the tissues in a variety of inflammatory processes in which fibrinoid degeneration also occurs. These processes included streptococcic and staphylococcic tonsillar and peritonsillar phlegmonous inflammations, diphtheria, chronic gastric ulcer, tuberculosis and gumma. In all of these, changes in the ground substance of the collagenous tissue are associated with the development of an argentophil property by the collagen fibrils. In this respect there is no essential difference between the tissue reaction of rheumatic fever and the other inflammatory processes investigated. One difference, which may be of help in determining the rheumatic character of a lesion, is that the argentophil fibrils of the rheumatic lesion persist for a long time and throughout the various stages through which the lesion passes, whereas in the other processes the fibrils undergo necrosis and disappear.

O. T. SCHULTZ.

CHANGES IN THE SCIATIC NERVE IN RHEUMATIC INFECTION. S. KOEPPEN, *Virchows Arch. f. path. Anat.* **286**:303, 1932.

Histologic examination of both sciatic nerves was made in thirty-seven necropsies for the purpose of determining whether changes occur in rheumatic fever and whether in sciatica changes occur that might be interpreted as the result of rheumatic infection. The material consisted of eight cases of acute and subacute rheumatic fever, nine cases of healed rheumatic infection, four cases of clinical sciatica, six cases of sepsis and ten miscellaneous control cases. In acute and subacute rheumatic fever the walls of the small vessels of the nerve were swollen, and there were numerous small, perivascular lymphocytic infiltrations. In three cases of clinical chronic sciatica the presence of recurrent valvular endocarditis was accepted as evidence of previous rheumatic infection. In these the artery of the nerve of the clinically involved side revealed atherosclerotic changes; the intima was thickened and the media calcified. In a case of acute sciatica without rheumatic stigmas thrombosis of the femoral vein had led to thrombosis of the veins of the nerve. In the cases of healed rheumatic infection and in the remaining cases no alterations were detected in the sciatic nerve.

O. T. SCHULTZ.

CHANGES IN THE UPPER AIR PASSAGES AND ESOPHAGUS IN RHEUMATIC FEVER.
D. SARAOFF, *Virchows Arch. f. path. Anat.* 286:314, 1932.

Gräff and Yoshitake have claimed that in rheumatic fever the infection enters by way of the tonsils and spreads downward through the lymphatics and tissue spaces into the organs of the neck. In seven unselected cases of acute and sub-acute rheumatic fever Sarafoff made a painstaking histologic study of the tissues of the pharynx, larynx, trachea and esophagus, down to the level of the bifurcation of the trachea. In six of the seven cases there were observed numerous characteristic focal rheumatic lesions, consisting in fibrinoid degeneration of the collagenous ground substance, cellular granulomas and scars. But the distribution of the lesions was not such as to uphold the view of Gräff and Yoshitake, and could be equally well interpreted as the result of widespread localization of the toxic-infectious agent by way of the blood stream.

O. T. SCHULTZ.

Microbiology and Parasitology

SEPTICEMIA IN THE NEW-BORN. ETHEL C. DUNHAM, *Am. J. Dis. Child.* 45: 229, 1933.

Thirty-nine cases of septicemia in new-born infants are reported. The commonest causative organisms were the streptococcus, the staphylococcus and the colon bacillus. Septicemia caused by streptococcus was frequently accompanied by cutaneous infections, omphalitis, meningitis and peritonitis and invariably resulted fatally. In cases of septicemia caused by staphylococcus or by colon bacillus, jaundice was common and the spleen was frequently enlarged. Anemia was less common in septicemia due to staphylococcus than in that caused by streptococcus or by colon bacillus. Infection of the urinary tract was found only in cases of septicemia due to colon bacillus. Neither septicemia caused by staphylococcus nor colon bacillus was invariably fatal. The author concludes that septicemia is an important and relatively frequent cause of morbidity and mortality in the new-born.

RALPH FULLER.

"COMMON COLD" IN SPITSBERGEN. J. H. PAUL and H. L. FREESE, *Am. J. Hyg.* 17:517, 1933.

A year's observation of respiratory diseases in the arctic mining town of Longyear City, Spitsbergen, indicates that the "common cold" is initiated by one or more specific, infective agents and that the disease is spread by direct contact. The period of incubation appeared to be about forty-eight hours. The clinical course of the disease varied in different persons who had presumably been exposed to the same "virus." Some persons seemed to have a complete immunity, while in others an immunity of short duration developed after an attack. This period was not shorter than twenty-three days in our series, and averaged seven weeks in the forty-nine persons who had had more than one attack at the time of our departure. The distribution of cases of the "common cold" by season is quite different from that reported for the temperate and tropical zones. The arrival of the first boat of the shipping season was followed by a sudden epidemic which involved almost the whole community in a short period of time. These epidemics are of annual occurrence. Our study indicated that an unfavorable environmental factor, such as a sudden drop in atmospheric temperature, is not necessary for the development of an epidemic. The study showed that the bacterial flora of the nasopharynx did not play any significant rôle in the initiation of the "common cold." Cultures from normal persons in Longyear City showed striking similarity to those obtained in the tropics and the temperate zone. The chief difference was that staphylococci and hemolytic streptococci were virtually absent in the population of Spitsbergen. This study confirms the fact that the fixed types of pneumococci and hemolytic streptococci are rarely encountered in isolated communities.

It also indicates that the various other groups of aerobic organisms isolated must be considered as normal inhabitants of the nasopharynx, since they occur in approximately equal percentages in normal throats in widely scattered geographical areas. It would be quite consistent with our observations to assume that the epidemic of "colds" described in this report was due to a filtrable virus of the type described by Dochez and his associates (*Lancet* 2:547, 1931) and by Long and his associates (*J. Exper. Med.* 53:447, 1931).

AUTHORS' SUMMARY.

EFFECT OF ENDAMOEBA HISTOLYTICA IN KITTENS. H. E. MELENEY and W. W. FRYE, *Am. J. Hyg.* 17:637, 1933.

A study has been made of the relative pathogenicity for kittens of two strains of *Endamoeba histolytica* from the hill country of the Eastern Highland Rim of Tennessee and of three strains from the lowland of West Tennessee. Three hundred and sixty-four kittens were inoculated by rectum or by ileum with cultures of these strains. In the first series of rectal injections, performed when the strains had been in culture between 17 and 132 days, the lowland strains from acute cases produced a much higher incidence of infection than did the two hill strains. The lowland carrier strain produced an incidence of infection about equal to the chronic hill strain. The second series of rectal injections, performed with four of the strains when they had been in culture between 253 and 262 days, gave about the same incidence of infection with all strains. There was some increase with the hill carrier strain and a decrease with the two lowland strains from acute cases. Injection of cultures directly into the ileum gave a higher incidence of infection with all strains than injection by rectum. With each of the two hill strains a few kittens known to have been successfully infected showed no macroscopic lesions at autopsy, whereas none of the kittens successfully infected with the three lowland strains were without macroscopic lesions at autopsy. Most of the kittens successfully infected with the hill strains showed only a few small lesions in the colon, whereas most of those infected with the lowland strains showed moderate or intense pathologic processes. When the duration of the infection in each kitten is considered, foregoing differences in the pathologic process still hold true. The lesions produced by each of the lowland strains apparently progressed with greater rapidity than those produced by the hill strains. These observations seem to indicate that strains of *E. histolytica* from different localities may show differences in the incidence of infection and in the amount of pathologic change produced in experimental animals. A somewhat higher incidence of infection in kittens was obtained with culture transplants 2 or 3 days old than with older transplants.

AUTHORS' SUMMARY.

REMOVAL OF GALL BLADDER IN TYPHOID CARRIERS. H. F. SENFTNER and F. E. COUGHLIN, *Am. J. Hyg.* 17:711, 1933.

Three hundred and sixty-eight chronic typhoid carriers have been discovered in upstate New York. The incidence of typhoid fever due to known carriers has been materially less subsequent to discovery as compared with the incidence prior to discovery. Removal of the gallbladder has resulted in the apparent cure of 59 per cent of those from whom required specimens have been submitted. The mortality among sixty-eight persons operated on was 14.7 per cent. If those in state institutions and those with acute gallbladder symptoms indicating operation are excluded, the mortality was 3.7 per cent. Sixty-eight per cent of those who survived the operation were apparently cured of the carrier condition. Removal of the gallbladder for the cure of chronic typhoid carriers should be advised only after careful consideration of the physical condition and age of the carrier and should not be advised unless preliminary duodenal specimens are positive.

AUTHORS' SUMMARY.

THE EFFECT OF IRRADIATED ERGOSTEROL ON CALCIFICATION OF TUBERCLES IN EXPERIMENTAL TUBERCULOSIS. M. JAMPOLIS and D. B. WITT, *Am. J. M. Sc.* **185**:338, 1933.

In two series of experiments intramuscular injections of a virulent culture of human tubercle bacilli were made into ten guinea-pigs, three serving as nontuberculous controls. In series B an attempt was made to simulate tuberculosis as it occurs in human beings. The procedure was the same as in series A, except that a preliminary injection of a known avirulent strain of human tubercle bacilli was given to all thirteen animals six weeks before the virulent culture was introduced. The effect of viosterol (administered orally) on the lesions produced was investigated. This demonstrated in a striking manner that the daily administration of viosterol in oil 1,000 X. in doses varying from 0.1 to 1 cc., causes deposition of calcium in the caseous tubercles in guinea-pigs. The blood of the animals so affected showed both hypercalcemia and hyperphosphatemia. There was no evidence of depletion of calcium in the roentgenograms of the bones. Spontaneous calcification did not occur in the tuberculous animals that received no viosterol. The most intense calcification was found in the lymph nodes and spleens of those tuberculous animals that were given the largest doses of viosterol. Deposits of calcium were noted only in the caseated areas. Undesirable calcification results if viosterol is given over a prolonged period in excessively large doses. In our investigation 0.2 cc. of viosterol in oil 1,000 X was administered daily for two months without any apparent harm. When continued for eighty-four days, undesirable calcification occurred. This dosage is equivalent to 6 cc. per kilogram of viosterol in oil 250 D. Calcification was present in the walls of the renal blood vessels and in the renal tubules of both the tuberculous and the nontuberculous animals that received daily amounts of viosterol in oil 1,000 X varying from 0.5 to 1 cc. for more than two months. No deposits of calcium were seen in the apparently normal portions of any of the other organs. The tuberculous animals that received the preliminary sensitizing injection did not show any definite calcification, possibly because the effect of viosterol is diminished in the presence of a fulminating secondary tuberculous process. The calcification of tubercles which was noted in this investigation is, in our opinion, not merely an expression of simple necrosis of the tissue but rather a reparative process. If it is permissible to calculate a human dosage of viosterol on a basis of weight, the maximum daily dosage given to our guinea-pigs corresponds to a dosage of 300 cc. of viosterol in oil 250 D, if given to a child weighing 22 pounds (10 Kg.). We refrain from making any recommendation concerning the clinical application of viosterol in tuberculosis because of possible renal damage. Future research may determine an optimum dosage which may have clinical value in certain types or stages of the disease.

AUTHORS' SUMMARY.

PRIMARY PERITONITIS COMPLICATING SCARLET FEVER. FERDINAND G. KOJIS and EDWARD J. MCCABE, *Am. J. M. Sc.* **185**:710, 1933.

A review of the literature shows that primary peritonitis complicating scarlet fever is a rare occurrence of grave prognostic importance. Three cases of this nature which developed in a series of 5,500 cases of scarlet fever occurring at the Willard Parker Hospital from 1928 to 1932 are reported. Most of the available evidence favors the blood stream as the route of transmission to the peritoneum, although many investigators favor the genital tract, in the female. A thick fibrinopurulent exudate covered the entire peritoneum in which the chief cell was the neutrophilic polymorphonuclear leukocyte. In two of the three cases culture of the peritoneal fluid yielded *Streptococcus haemolyticus*. SANDER COHEN.

HERPETIC INFECTION OF THE CHORIO-ALLANTOIC MEMBRANE OF THE CHICK EMBRYO. J. R. DAWSON, JR., *Am. J. Path.* **9**:1, 1933.

The chorio-allantoic membranes of the chick embryo are susceptible to infection with a strain of herpes simplex virus which is innocuous to adult chickens of the

same breed. The microscopic lesions of these membranes are like those of herpetic lesions of mammals. A peculiar nuclear change in ectodermal cells is described, characterized by enormous enlargement of the nucleus, and by a partitioning of it by delicate trabeculae into compartments which are filled by minute, uniform and faintly stained basophilic granules.

AUTHOR'S SUMMARY.

CELLULAR INCLUSIONS IN LETHARGIC ENCEPHALITIS. J. R. DAWSON, JR.,
Am. J. Path. 9:7, 1933.

A case of epidemic encephalitis is reported in which intranuclear and intracytoplasmic "inclusions" occur. It is suggested, on the basis of the presence of cellular inclusions, that this case of encephalitis may have been due to a cytotropic virus. Two other cases of encephalitis are mentioned in which no inclusions were found. It is further judged from an etiologic standpoint that epidemic encephalitis may not be a distinct entity. Inoculations into animals with material from each case induced no demonstrable infection.

AUTHOR'S SUMMARY.

LIVER ABSCESES CAUSED BY A LEPTOTHRIX, WITH A REVIEW OF LEPTOTHRICAL INFECTION. P. N. HARRIS, Am. J. Path. 9:71, 1933.

A summary of the literature pertaining to leptothrices pathogenic to man is presented. Report is made of a case of leptotrichosis in which multiple abscesses of the liver were formed, with rupture of one abscess into the base of the right lung and formation of an abscess of the lung, and rupture of another abscess in the left lobe of the liver, leading to the production of pericarditis. The organism was isolated in pure culture from the liver and successfully carried in vitro through many generations. No other organisms were present in the lesions. Experimental work with the organism showed it to be slightly pathogenic for rabbits and guinea-pigs. This organism has apparently never been previously encountered.

AUTHOR'S SUMMARY.

HISTOLOGICAL STUDY OF A CASE OF THE EASTERN TYPE OF ROCKY MOUNTAIN SPOTTED FEVER. P. N. HARRIS, Am. J. Path. 9:91, 1933.

The occurrence of Rocky Mountain spotted fever in Tennessee and a histologic study of a fatal case are herewith reported. The occurrence of lesions of the brain in the Eastern form of Rocky Mountain spotted fever reported by Lillie is confirmed. Attention is called to a type of lesion of the brain which may prove to be diagnostic of the Eastern form of Rocky Mountain spotted fever.

AUTHOR'S SUMMARY.

THE MICROINCINERATION OF INTRANUCLEAR INCLUSIONS IN YELLOW FEVER. E. V. COWDRY, Am. J. Path. 9:149, 1933.

In preparations of uninjured liver cells of the monkey made by micro-incineration, as specified in this article, the nuclear ash corresponds closely in position with materials seen in the fresh cells, as well as in fixed and stained preparations. The nucleolus, easily recognizable in fresh cells by its position, shape and refractive index, is found to be amphophilic in fixed and stained specimens and to yield a heavy, sharply localized ash after incineration. Chromatin, which is not visible as such in the still living cell but can be observed after fixation and staining in the form of basophilic substance scattered in the nucleoplasm and applied to the nuclear membrane, also leaves a mineral residue which is rather less dense. Marked alterations occur in nuclei reacting to the virus of yellow fever and in which nuclear inclusions are developing. The changes in size and shape of the nuclei, in the basophilic chromatin and in the nucleolus, described by Cowdry and Kitchen in stained preparations, can be followed with almost equal precision in the

incinerated specimens because parallel modifications occur in the mineral residue. But the nuclear inclusions, pathognomonic of the disease, although conspicuous features of the fresh and fixed and stained preparations, cannot be studied in incinerated specimens for they yield little or no ash. They therefore differ from the nucleoli and from basophilic chromatin in the same way that Scott observed in the case of nuclear inclusions caused by the action of the submaxillary virus in guinea-pigs.

AUTHOR'S SUMMARY.

VACCINE VIRUS PNEUMONIA IN ANIMALS. H. A. McCORDOCK and R. S. MUCKENFUSS, *Am. J. Path.* **9**:221, 1933.

Vaccine virus injected into the lungs of rabbits, when strong, causes a hemorrhagic, edematous consolidation and irregular areas of necrosis; diluted, the virus causes interstitial infiltration with mononuclear cells. The first type of lesion is similar to the lesion found in the lungs of persons dying early in an attack of influenza. The second type of lesion resembles the interstitial cell infiltration of the bronchopneumonia in influenza, measles and whooping cough, with the bronchopneumonic exudate lacking, but this can be produced also by injecting bacteria after the introduction of the dilute vaccine virus. The authors regard interstitial bronchopneumonia as "the type reaction for the combination of a virus and bacteria, although in no sense specific for a particular virus or bacterium."

TUBERCULOSIS AND LEUKEMIA. R. H. JAFFE, *Am. Rev. Tuberc.* **27**:32, 1933.

The author describes three cases of myelogenous leukemia in which autopsy disclosed the activation of an old and apparently silent tuberculosis. The first patient died from an acinous nodose pulmonary tuberculosis which had markedly influenced the leukemia, improving the anemia and decreasing the number of white cells in the peripheral blood. Extramedullary myelopoiesis was restricted to the spleen. In the second case tuberculous peritonitis developed from tuberculous lesions in the peripancreatic lymph nodes. The tuberculosis had no effect on the leukemia. In these two instances the histologic picture of the tuberculous changes did not reveal any peculiarities, and typical epithelioid cell tubercles with giant cells were found. The third case showed a recent caseating tuberculosis of the right suprarenal, which was an accidental finding and was apparently secondary to the flaring up of an old focus in the right submaxillary lymph nodes. The suprarenal process showed a predominance of necrosis of the primary tissue and a lack of cellular response. There were no evidences that the leukemic cells took part on the defense reactions against the infection.

H. J. CORPER.

LOCALIZED EXPERIMENTAL TUBERCULOSIS OF THE LUNGS. ROBERT G. BLOCK, *Am. Rev. Tuberc.* **27**:143, 1933.

To produce localized pulmonary tuberculosis tubercle bacilli suspended in iodized oil are introduced into the trachea through an incision in the neck, a short needle on a tuberculin syringe being used with roentgenographic control of the localization of the infection. The method allows the production of localized primary tuberculous complexes with virulent bacilli. It can be used with advantage for experiments requiring slowly progressive lesions with late secondary involvement.

H. J. CORPER.

A COMPARISON OF CERTAIN MEDIUMS FOR THE CULTIVATION OF TUBERCLE BACILLI FROM SPUTUM. M. F. SHAFFER, *Am. Rev. Tuberc.* **27**:259, 1933.

The author studied six different mediums as to their relative value for the cultivation of the tubercle bacillus from sputum, following preliminary treatment with 6 per cent sulphuric acid according to a slightly modified Corper-Uyei method. The potato medium of Corper and Uyei yielded the largest number of positive reactions, with the Petragnani medium (of milk, potato and egg) yielding results

nearly as good. These two mediums were superior to the other four mediums tried as to the number of positive reactions. Lubenau's medium (of eggs) proved slightly superior to Dorset's (egg), Petroff's (veal infusion egg) and Sweany and Evanoff's (milk, veal and egg) mediums. Dissociation of the primary cultures into colonies resembling the so-called R and S types was noted particularly on Petroff's medium.

H. J. CORPER.

A COMPARISON OF TISSUE REACTIONS TO PULMONARY INFECTION WITH TUBERCLE BACILLI IN ANIMALS OF VARYING RESISTANCE. ARTHUR J. VORWALD, *Am. Rev. Tuberc.* **27**:270, 1933.

Tubercle bacilli of the human type in the proportion of 0.1 mg. per kilogram of body weight are injected intravenously into guinea-pigs, monkeys, dogs, rabbits, rats, cats and chickens. In all cases the pulmonary tissue, in contrast to the intrapulmonic lymphoid tissue, retained a major portion of intravenously injected tubercle bacilli, and the initial cellular reaction occurred at the point of lodgment of the organisms. The lymphoid structures of the lung were involved only secondarily. The susceptibility of the animals studied, as indicated by the measured extent of the individual cellular reactions, showed decided variations. The guinea-pig and the rabbit, although in the beginning responding with an equally intense reaction, ultimately differed greatly as to the amount of tuberculous tissue developed. The guinea-pig at one month proved to be a most susceptible animal and the rabbit a much more resistant one. The rat and the chicken, on the other hand, responding early with a reaction slightly less than that in the guinea-pig and rabbit, at one month showed decidedly more resistance. The monkey and dog, which at one day showed a minimal response, less than that in any of the aforementioned animals, at the final period proved to have less extensive tuberculous reaction than the guinea-pig, but much more than the rabbit, rat or chicken. The cat, the remaining animal of the series, reacted most sluggishly in the beginning, but, unlike the monkey and dog, in the final outcome proved a most resistant animal. The variations in susceptibility therefore did not parallel the intensity of the initial cellular reaction. In the guinea-pig, rabbit and rat the polymorphonuclear neutrophilic leukocyte played an important part in localizing the tubercle bacilli. Subsequently these leukocytes with their bacillary content were commonly phagocytosed by large mononuclear exudate cells. In the more mature reactions the mononuclear-exudate cell was the predominant type in all animals. No relation was detected between these mononuclear-exudate cells and the susceptibility of the individual species studied. There was an evident quantitative and also a qualitative difference in reactivity of the species—a quantitative one as shown by the difference in size of the cellular responses and a qualitative one in that in certain species polymorphonuclear leukocytes persisted in the responses throughout all periods. In other species these cells took little part in the later reactions, and in the chicken, a resistant animal, they were absent in the response at the one month period. No constant relationship was found between caseation and any particular type of cellular reaction.

H. J. CORPER.

HOT BATHS IN EXPERIMENTAL SYPHILIS OF RABBITS AND IN TRYPANOSOMIASIS OF RATS. JOHN A. KOLMER and ANNA M. RULE, *Arch. Dermat. & Syph.* **27**:660, 1933.

The authors infected rabbits intratesticularly with *Spirochaeta pallida* and four days afterward started daily immersion of the entire body, with the exception of the head, in water at 45 C. (113 F.) for twenty minutes. This resulted in prevention of testicular syphilis, and spirochetes could not be demonstrated in the inguinal lymphatic glands by animal inoculation. If the testicles were kept out of the water, syphilis developed in the usual way. They believe, therefore, that the sterilizing effects of hot baths are local rather than general. Similar immersion of rats infected with *Trypanosoma equiperdum* did not retard or prevent the development of fatal trypanosomiasis.

S. W. BECKER.

EXOGENOUS TUBERCULOUS INFECTION OF ADULTS. EUGENE L. OPIE and F. MAURICE MCPHEDRAN, Arch. Int. Med. 50:945, 1932.

When roentgenographic methods are used for the recognition of tuberculous lesions of the lungs in spouses in contact with a tuberculous partner, exogenous infection of adults is clearly demonstrable. Husbands and wives in marital contact with tuberculosis under varying conditions are infected from five to nine times as often as persons with no known contact with the disease; husbands are infected oftener than wives. The frequency of infection in wives exposed to husbands with tubercle bacilli in the sputum was 35.5 per cent; in those exposed to husbands with no demonstrable tubercle bacilli, 22.9 per cent. The incidence of infection in husbands exposed to wives with open tuberculosis was 45.6 per cent, and when there were no tubercle bacilli in the sputum it was 35.9 per cent. When the incidence of latent apical tuberculosis in persons exposed to the disease in husband or wife is compared with that in husbands or wives with no known exposure to tuberculosis, the possibility that the difference has occurred by chance is negligible.

AUTHORS' SUMMARY.

BACTERIOLOGY OF ABSCESS OF THE LUNG AND METHODS FOR ITS STUDY. J. COHEN, Arch. Surg. 24:171, 1932.

The subject of the bacterial flora of abscesses of the lung is reviewed. The technic of the cultivation of material from the abscesses is considered, with particular reference to anaerobiosis. Sixteen cases were investigated. Diphtheroids and "doubtful" anaerobic streptococci were present in each case. Bacterium melaninogenicum was next in frequency. A large variety of anaerobic bacilli were found. Definite conclusions as to the significance of the organisms were not reached.

N. ENZER.

MONOSPOROSIS (MADURA FOOT). M. GELLMAN and J. A. GAMMEL, Arch. Surg. 26:295, 1933.

A third case of infection of the foot by *Monosporium apiospermum* in a native white American is described under the name of monosporosis. The clinical picture was that of mycetoma or madura foot.

PERLÈCHE. M. H. GOODMAN, Bull. Johns Hopkins Hosp. 51:276, 1932.

A specific etiology of perlèche has not been determined. A case of chronic perlèche in an adult is reported, and also one of an acute type in a child. A survey of the literature and a cultural study of the two cases would suggest that perlèche may be primarily produced either by streptococci and staphylococci or by a fungus organism. However, there remains the possibility that an as yet undiscovered virus is the primary agent and that these organisms are secondary invaders. Histologic examination in the cases studied showed a chronic granuloma.

AUTHOR'S SUMMARY.

THE PATHOGENESIS OF TUBERCULOUS MENINGITIS. A. R. RICH and H. A. MCCORDOCK, Bull. Johns Hopkins Hosp. 52:5, 1933.

Experimental and morphologic evidence is presented which demonstrates that diffuse tuberculous meningitis is not a direct and immediate result of hematogenous infection of the meninges. Miliary tuberculosis produces only rare, sparsely scattered tubercles in the meninges, not diffuse meningitis. Tuberculous meningitis has its origin in the discharge of bacilli into the cerebrospinal fluid from adjacent older caseous foci of the infection. Such discharging foci have been found, by careful search, in the substance of the brain or cord, in the meninges, in the bones encasing the central nervous system or in the choroid plexus in seventy-seven of

the eighty-two cases of meningitis in our series. In all except two of these seventy-seven cases, the source of the diffuse meningitis was situated in the substance of the central nervous system or in the meninges. In the five cases in which no discharging focus was found, the material for study was incomplete.

AUTHORS' SUMMARY.

EFFECT OF OLIVE AND COD LIVER OILS ON TUBERCULOSIS. L. NÈGRE, *Ann. Inst. Pasteur* **49**:319, 1932.

Guinea-pigs inoculated subcutaneously with bovine or human tubercle bacilli and treated by injections of olive oil showed more pronounced lesions than controls. These signs were apparent in certain larger nodes, in more numerous and more extended lesions in the spleen, and, in some cases, in involvements of the liver, lungs or bronchial nodes not marked in controls. The results with cod liver oil were somewhat similar. More numerous lesions were also observed in rabbits treated by injections of olive oil and cod liver oil. Sterilized and natural olive oils acted in the same manner.

M. S. MARSHALL.

EXPERIMENTAL MENINGEAL SPIROCHETOSIS. J. TROISIER, *Ann. Inst. Pasteur* **49**:343, 1932.

The subdural inoculation of *Leptospira icterohaemorrhagiae* produced in guinea-pigs acute fatal meningitis with or without icterus. There was a cellular reaction (mononuclears and polymorphonuclears) often accompanied by a local multiplication of spirochetes. Young rabbits gave similar responses, whereas in young dogs there developed either a benign curable meningitis appearing after six or eight days, with fever for a week following cure, or a malignant type with precocious cachexia and diffuse myoclonia. In both types of infection in the dogs there were a hypercytosis of the cephalorachidian fluid and an increase in albumin. In lower monkeys, when spirochetes had been injected into the cephalorachidian fluid, fever developed after a short period of incubation, and the animal became emaciated, without icterus. Thus, the reality of meningeal spirochetosis without icterus, as clinically observed in man, is proved with the spirochete of infectious jaundice.

M. S. MARSHALL.

NATURAL HISTORY OF TYPHUS. H. MOOSER, *Arch. Inst. Pasteur de Tunis* **21**:1, 1932.

Based on studies of the vectors and the behavior in animals of strains of the typhus virus, the question of the natural history of the viruses of the Old and New World is considered. A Tunis strain multiplied in several varieties of fleas, but less regularly than a Mexican strain. Animals in a series in which the infection was started by bites of fleas showed fever and scrotal and cerebral lesions. Material from the latter showed no modification in the fever or period of incubation of inoculated animals. By rat-flea-rat passage most of the effects produced by Mexican strains were duplicated by Tunis strains. Differences seemed likely to be due to the hosts of the virus. Strains undergoing a rat-flea-rat passage during endemic periods (with low mortality) had qualities that were different from those of the man-flea-man strains of epidemic times (with high mortality). The possible significance of rats as reservoirs is considered great, and it is suggested that the Tunis virus, through longer adaptation, has lost some of the original properties manifested by the Mexican variety. Two addenda to the article make note of a report of a virus found in Greece which is similar to the American type, confirming the author's views, and of a report (April, 1932) of a Manchurian strain said to be specific, which the author criticizes as indicating no new strain.

M. S. MARSHALL.

COMMON ORIGIN OF TYPHUS AND OTHER EXANTHEMATIC FEVERS. CHARLES NICOLLE, Arch. Inst. Pasteur de Tunis 21:32, 1932.

"To summarize in a phrase this long dissertation, we think, as does Moser, that these two typhus fevers (Old and New World) have a common origin; but we do not believe that one may transform itself into the other and that the hypothesis may be advanced that there exists only one typhus fever."

M. S. MARSHALL.

INFLAMMATORY EPITHELIAL REACTIONS OF ASCARIS. G. LÜBINSKY, Virchows Arch. f. path. Anat. 285:691, 1932.

In higher animals study of epithelial reactions to inflammatory agents is complicated by the fact that epithelium is always associated with connective tissue, in which the most marked inflammatory reactions occur. Study of the reactions of epithelium alone is possible in those lower forms that contain no connective tissue, namely, hydroids and nematodes. In various species of *Ascaris* there occurs a disease known as dermomyositis. A study of this condition in the swine parasite (*A. suum*) is presented by the author. The body wall of the parasite consists of an outer chitinous cuticle, a syncytial epithelial hypodermis and a layer of longitudinal smooth muscle fibers. To injury or infection from without, the epithelium reacts by hypertrophy, hyperplasia and downgrowth into the underlying smooth muscle. The cuticle becomes thickened and isolates the invading micro-organism or the area of injured tissue. The isolating mass of cuticle is then sequestered and cast off.

O. T. SCHULTZ.

VIOSTEROL IN TUBERCULOSIS. KÄTHE JÄGERMANN, Virchows Arch. f. path. Anat. 285:764, 1932.

The oral administration of viosterol did not lead to calcification of caseous lesions or to increased connective tissue reaction about the tubercles in experimental tuberculosis of guinea-pigs. The histologic changes in the lungs of ten persons with pulmonary tuberculosis who had been treated with the vitamin preparation did not differ from those in eleven persons who had not received the oil. In the aortas of the patients who had been treated with irradiated oil there were observed changes that may have been due to the toxic action of the preparation.

O. T. SCHULTZ.

A CASE OF CONGENITAL TUBERCULOSIS. H. CHIARI, Virchows Arch. f. path. Anat. 285:779, 1932.

Necropsy of an infant 13 weeks old confirmed the clinical diagnosis of general miliary tuberculosis and tuberculous meningitis. The tubercles, which were most numerous in the lungs, liver and spleen, were barely visible to the naked eye and were translucent. In the left lung was a partly calcified primary complex. In the liver were six partly calcified lesions, apparently as old as the primary focus in the lung. The lymph nodes at the hilus of the liver were caseous and partly calcified. The involvement of the liver and its nodes is also considered to have been a primary complex, as old as that of the lung. The author believes that infection occurred during the late intra-uterine period and led to primary involvement of the liver and the left lung.

O. T. SCHULTZ.

CULTIVATION OF TUBERCLE BACILLI FROM THE BLOOD AT NECROPSY. H. POPPER, F. BODART and W. SCHINDLER, Virchows Arch. f. path. Anat. 285:789, 1932.

Cultivation of the cardiac blood at necropsy yielded tubercle bacilli in two of three early cases and in ten of eleven late cases of general tuberculosis. Eighteen of twenty cases of progressive pulmonary tuberculosis, in which the disease was

the cause of death, yielded positive results. In eight cases of progressive, nonfatal pulmonary tuberculosis and in thirty-three of stationary pulmonary tuberculosis, the results were negative. The bacilli were cultivated from the blood in a case of urogenital tuberculosis with a fatal outcome due to meningitis. Eight cases of organic tuberculosis, in which tuberculosis was not the cause of death, and three cases of polyserositis yielded negative results.

O. T. SCHULTZ.

Tumors

EXPERIMENTAL TOBACCO-CAUSED METAPLASIA OF THE GASTRIC MUCOSA OF THE DOG. A. MORATTI, Tumori 6:101, 1932.

An attempt was made to reproduce smoker's plaques and "tobacco epitheliomas" in dogs and mice. A small portion of the stomach was isolated and repeatedly treated with tobacco fumes and a concentrated solution of nicotine. After two years typical plaques of cornified squamous epithelium could be observed in the mucous membrane of the isolated part of the stomach. No malignant growth was produced. The author considers the irritating effect of the nicotine as the cause of the metaplasia, and presumes that a second, internal factor is necessary for the development of a malignant growth.

E. VON HAAM.

LOCAL EFFECT OF INSULIN ON CANCER OF THE SKIN. S. F. GOMES, Tumori 6:140, 1932.

The local application of insulin on ulcerated cancers of the skin produced healing of the ulcers and partial disappearance of the malignant growth. The epithelium which covered the treated ulcers was similar to normal squamous epithelium, and the neoplastic tissue on the margin of the ulcers underwent regressive, fibrous changes. In one case three fifths of the tumor disappeared under the treatment. Cancer of the skin seems to possess a specific sensibility for insulin; in this respect it differs from the medullary forms of carcinoma.

E. VON HAAM.

CATALYTIC ENZYMES OF THE BLOOD IN MALIGNANT TUMORS. A. LOREURI, Tumori 6:201, 1932.

The author studied the volume of catalytic enzymes in the blood of patients with cancer before and after roentgen therapy. He found that there were fewer enzymes in the blood of patients with cancer than in the blood of controls. After roentgen therapy the volume of catalytic enzymes dropped considerably, probably because of the toxic effect of the destroyed tumor cells.

E. VON HAAM.

CHOLINE METABOLISM IN MICE WITH ADENOCARCINOMA. A. BOLAFFI, Tumori 6:209, 1932.

The choline content of the growth and of the tissues of the animals inoculated with the tumor was studied and compared with that of normal controls. A steady increase of free choline was found in the growing tumor up to the twenty-fifth day of its growth. Thereafter the choline in the tumor tissue began to disappear, and only a slight increase could be found at the time of death. The choline curve of the animals with tumors showed a continuous decrease up to the time of death.

E. VON HAAM.

VALUE OF THE ASCHHEIM-ZONDEK REACTION IN THE DIAGNOSIS OF TUMORS. M. FERRO, Tumori 6:314, 1932.

The author repeated the experiment of Engel, who reported the presence of secretion of the pituitary gland in the urine of patients with cancer. The technic of this test is the same as that of the Aschheim-Zondek test for pregnancy. In an examination of eighty patients with cancer the results were completely negative. The author therefore denies the value of this test in the diagnosis of cancer.

E. VON HAAM.

HISTOLOGIC CHANGES IN LYMPH GLANDS IN CANCER. N. MONTANINI, *Tumori* 6:328, 1932.

The author studies the histologic picture of 800 lymph glands from 280 patients with cancer. Three groups of reaction are described. One group of glands showed an inflammatory reaction with hyperemia and hyperplasia of the lymphatic tissue. A second group showed marked hyperplasia of the reticulo-endothelial apparatus. In the third group marked fibrosis with atrophy of the glandular tissue was evident. Metastasis was found mainly in the third group. The first group showed a few malignant cells in the sinus, and the second group was always free from metastasis. The hyperplasia of the reticulo-endothelial cells in lymph glands of patients with cancer represents, therefore, a strong defensive reaction in the glands which protects them from invasion by the tumor cells.

E. VON HAAM.

REACTION OF BONE TISSUE FOLLOWING ADJACENT INOCULATION OF TUMORS. D. MUCCI, *Tumori* 6:501, 1932.

In mice and adult rats the inoculation of sarcoma in parts near the skeleton leads, first, to a proliferative reaction of the bone substance, followed by marked retrogressive changes. The proliferative reaction is produced by the periosteum of the bone and consists of callus-like formations, except that there is a remarkable disorganization in the histologic structure. The retrogressive changes affect the newly formed tissue as well as the preexisting osseous substance. The compact osseous substance is destroyed by lacunar reabsorption. The spongy bone substance undergoes fragmentation of the trabeculi. The appearance of multinucleated giant cells can be explained as a local reaction and can always be seen when the tumor penetrates the bone marrow. Finally, the picture of an osteoid sarcoma is produced.

E. VON HAAM.

THE CANCER CONSTITUTION. A. MORATTI, *Tumori* 6:573, 1932.

The existence of a cancer constitution is an important discovery. The malignant tumor represents only a local symptom of a general metabolic disease of the organism. The experiments with tar cancer with different degrees of success in various animal groups make the existence of such a cancer constitution probable. The metabolic changes in patients with cancer have been thoroughly studied, and many interesting findings have been reported. Changes in the mechanism of the internal secretion and in the physicochemical reaction of the body fluids have been believed to be a sign of the existence of such a disposition. Cholesterol and carbohydrate metabolism, the relationship of calcium and potassium to tissue and body fluids and the albumin-globulin factor of the blood are found to undergo marked changes in patients with new growths. Warburg, Waterman and others in their fundamental experiments on the metabolism of the cancer cell are not able to explain fully the metabolic changes in the organism in the initial state of cancer. The existence of a constitution which forms a disposition to the development of cancer might also explain the frequent recidivation after surgical removal of a cancer, the multiplicity of malignant growths in the same person, as reported often in the literature, and the complicated mechanism of selective metastasis.

E. VON HAAM.

MICRODISSECTION STUDIES OF MALIGNANT AND NONMALIGNANT TISSUE CELLS. ROBERT CHAMBERS and R. J. LUDFORD, *Arch. f. exper. Zellforsch.* 12:555, 1932.

On testing mammary gland and mammary carcinoma cells, embryo skin cells and cells from transplantable tar carcinoma, fibroblasts, sarcoma cells and macrophages according to the microdissection method, it was found that there are no differences in consistency between cancer cells and their nonmalignant prototypes. The two kinds of cells react to mechanical injury in the same manner. Puncture

of the nucleus always resulted in collapse and coagulation, followed by the death of the cell. Epidermal cells growing in sheets are firmly bound together, and the sheets may tear with no respect to cell boundaries. The epithelial cells of tar carcinoma adhere less firmly. Mammary cells, normal and cancerous, adhere, and, when separated, glutinous strands stretch between them. Fatty globules within the cytoplasm of mammary gland cells possess a membranous investment which can be wrinkled and torn with microneedles.

AUTHORS' SUMMARY.

MALIGNANT PINEALOMA AND MALIGNANT FETAL ADENOMA OF THE HYPOPHYSIS.

E. KUX, Beitr. z. path. Anat. u. z. allg. Path. **87:59**, 1931.

A man, aged 22, had an infiltrating plum-sized pinealoma which showed cells of two types: small lymphocyte-like cells such as are normally present in the fetal and new-born pineal gland, and large cells, rich in cytoplasm, which probably developed from the former. Evidence of an internal secretory disturbance was lacking.

A man, aged 32, presented a 5 cm. suprasellar malignant fetal cell adenoma which compressed the base of the third ventricle. Clinically, there was evidence of local cranial changes plus mild acromegalic changes in the terminal phalanges. Hemorrhage into the tumor produced amaurosis and diabetes insipidus twenty-four hours before death from rupture into the ventricles.

W. S. BOIKAN.

MULTIPLE LIPOMAS OF THE SMALL BOWEL. A. ESSER, Centralbl. f. allg. Path. u. path. Anat. **55:6**, 1932.

Eight lipomas were found in 20 cm. of the jejunum of a 77 year old woman who had died of cardiac decompensation. The largest of these was the size of a cherry; the others were as large as a pea. They lay within the submucosa and were separated from the mucosa and muscularis by a layer of connective tissue. The bowel was involved in a marked chronic passive hyperemia, but this condition was lacking in the tumors, although the capsule of the largest of these was edematous. Except for the absence of rugae over the masses and occasional collections of small lymphocytes, the bowel in the vicinity of the tumors was unaltered.

GEORGE RUKSTINAT.

A HYPERNEPHROID ADENOMA OF THE LIVER WITH INCLUSIONS OF BONE. G. PATRASSI, Centralbl. f. allg. Path. u. path. Anat. **55:37**, 1932.

A friable tumor was found in the right lobe of the liver of a 67 year old man who had died of bronchopneumonia. The periphery of the tumor was composed of tissue resembling suprarenal cortex; its midzone was a voluminous mass of homogeneous hyaline material, and its center contained blood vessels, islands of bone marrow and cords of bone and osteoid tissue. Patrassi discusses the current theories of the origin of ectopic myeloid tissue and then contributes the following one: The vessels of the suprarenal medulla arise from the primordial kidney, and the branches of these vessels, which grow into the interrenal body, could in rare instances associate themselves with multipotent mesenchymal centers which later could produce bone marrow and bone. The presence of large blood lacunae and angiomatous regions in certain of these tumors seems to lend credence to the theory. No explanation is offered for the occurrence of such changes in the liver, however.

GEORGE RUKSTINAT.

A CASE OF MULTIPLE MYELOMA (PLASMOCYTOMA). J. B. PORCHOWNIK, Virchows Arch. f. path. Anat. **280:534**, 1931.

In the Russian literature only three cases of multiple myeloma have been reported. The author adds a fourth from the Government Roentgen-Radium Institute in Kiev, with a discussion of the pathology, clinical features, therapy and roentgenologic observations.

PERRY J. MELNICK.

TERATOID ABDOMINAL TUMORS OF THE FOWL. Ü. MASHAR, *Virchows Arch. f. path. Anat.* 285:155, 1932.

The author describes two abdominal teratoid tumors of the fowl and tabulates eleven previously reported similar neoplasms. The tumors reached a relatively large size and exhibited variations in structure from well differentiated derivatives of the three germ layers to embryonal carcinomatous tissue. With one exception, the tabulated neoplasms occurred in cocks, chiefly in young ones. They arose in the testis, kidney or peritoneum. The tumor in a hen originated in the ovary. The author believes that the tumors originate in the celomic epithelium.

O. T. SCHULTZ.

OSTEOPLASTIC SECONDARY CARCINOMA OF THE LUNG. W. LAUBMANN, *Virchows Arch. f. path. Anat.* 285:169, 1932.

In a case of inoperable carcinoma of the stomach in a man, aged 65, the lungs contained multiple metastases. Histologically, the metastases were composed of bone, osteoid tissue, cartilage and chondroid tissue. The tissues arose by metaplasia of the fibrous stroma of the metastases, brought about supposedly by the chemical stimulus of the tumor cells.

O. T. SCHULTZ.

INCIDENCE OF PRIMARY CARCINOMA OF THE LUNG AND BRONCHI. E. SIMMROSS, *Virchows Arch. f. path. Anat.* 285:183, 1932.

The impression that the incidence of primary carcinoma of the lung and bronchi has increased in recent years was tested by an analytic study of the necropsy material in Gruber's institute in Göttingen. As the increase is supposed to have occurred since the war and the influenza pandemic of that time, the incidence of pulmonary carcinoma in 1,100 consecutive necropsies made from 1906 to 1912 is compared with that in an equal number of necropsies made from 1927 to 1931. Only necropsies of persons over 15 years of age were included. In the period from 1906 to 1912, the total number of cases of carcinoma was 194, or 17.63 per cent. There were 5 primary carcinomas of the lung, i. e., 0.45 per cent of the necropsies and 2.59 per cent of all the cases of carcinoma. In the period from 1927 to 1931, there were 173 cases of carcinoma, or 15.72 per cent. During this period there were 17 primary carcinomas of the lung; these constituted 1.55 per cent of the total necropsies and 9.83 per cent of all the carcinomas. The increase during the postwar period was progressive and reached its maximum in 1931, when 6, or 27.27 per cent, of 22 cases of carcinoma coming to necropsy represented primary pulmonary or bronchial carcinoma. The sex ratio in Simmross' series was 4.5 males to 1 female. In 900 cases tabulated from the literature, the ratio was 3.22 males to 1 female. In the Göttingen series, the right lung was involved in 12 cases, the left in 7 and both lungs in 3.

O. T. SCHULTZ.

PIGMENTED NEVI IN THE EPIDERMIS OF OVARIAN DERMoids. O. LUBARSCH, *Virchows Arch. f. path. Anat.* 285:197, 1932.

Lubarsch refers to observations made originally twenty-six and twenty-four years ago to record the presence of pigmented nevi in the epidermis of ovarian dermoids of two women aged 80 and 61, respectively. The older woman had numerous pigmented and vascular nevi of the skin. Further search brought to light a vascular nevus of the dermoid epidermis. The senile character of the epidermis of the dermoid in this case and the loss of pigment from the hair of the dermoid, together with the nevi, favor the Marchand-Bonnet theory that the ovarian dermoid is derived from the same fertilized ovum that gives rise to the bearer of the dermoid, and that the dermoid is the single ovum twin of the woman who has the dermoid rather than her parthenogenetic offspring.

O. T. SCHULTZ.

HYPERNEPHROMA OF THE KIDNEY. L. PUHR, *Virchows Arch. f. path. Anat.* **285:291**, 1932.

Puhr describes eight tumors of the kidney belonging to the group usually termed hypernephroma, a designation to which the author objects. The presence of fat, glycogen and hemoglobin derivatives in the tumor cells is an expression of their specialized functional activity and is not due to regressive changes. These evidences of vital storage, together with the morphology of the tumor cells and their relation to the capillaries of the tumor, place the Grawitz tumor in the group of reticulo-endotheliomas.

O. T. SCHULTZ.

INCIDENCE OF TUMORS OF THE BRAIN. V. RUDERSHAUSEN, *Virchows Arch. f. path. Anat.* **285:318**, 1932.

Not the least interesting feature of this article is that it is based on the necropsy protocols from 1854 to 1931, inclusive, at the pathologic institute of the University of Heidelberg. Records for the years 1855 to 1862, inclusive, and 1864 are missing, but from 1865 on the series is complete. The total number of necropsies was 31,698. The total number of tumors of the brain was 546, or 1.72 per cent of all the necropsies. There were 444 (1.4 per cent of the total necropsies) primary and 102 secondary tumors of the brain. Of the primary tumors, 232 were classified as gliomas. The proportion of male to female patients was 5:4 for primary tumors, 4:3 for secondary tumors and 3:2 for gliomas. The largest number of primary tumors occurred in the fifth decade, and of the secondary tumors, in the sixth. The highest age incidence of glioma was from 45 to 50 for male patients and from 40 to 45 for female patients. The collective statistics of other observers are presented by the author.

O. T. SCHULTZ.

A CASE OF MULTIPLE TUMORS OF THE CENTRAL NERVOUS SYSTEM. RUTH KATZENSTEIN, *Virchows Arch. f. path. Anat.* **286:42**, 1932.

Necropsy of a man, aged 28, revealed multiple tumors of the dura of the brain and cord, bilateral tumors of the acusticus, multiple tumors of the posterior roots of the spinal nerves and multiple tumors of the substance of the cord from the cervical region to the cauda. The tumors of the cord had caused no symptoms. The symptoms, which had been slowly progressive for half a year, were due to one of the tumors of the cerebellopontile angle, for which operation was attempted. The tumors of the dura were fibro-endotheliomas, some of which contained calcified psammoma bodies. The tumors of the nerve roots were neurinomas and neurinofibromas. The interstitial tumors of the cord were differentiated gliomas. The central canal of the cord was dilated and surrounded by a zone of diffuse gliosis derived from incompletely differentiated ependymal cells that lined the canal. In the skin of the abdomen were three small fibromas. The case is called one of internal Recklinghausen's disease. The condition is held to be the result of embryonic maldevelopment.

O. T. SCHULTZ.

MAMMARY FIBRO-ADENOMA OF THE LABIUM MINUS. R. FRIEDEL, *Virchows Arch. f. path. Anat.* **286:62**, 1932.

A globular tumor nodule 3 cm. in diameter, covered externally by wrinkled skin, was attached by a long narrow pedicle to the labium minus of a woman aged 22. The growth had been present since the fourteenth year of her life. The histologic structure was that of a fibro-adenoma of the mammary gland. The tumor is believed to have arisen in a misplaced, supernumerary mass of mammary tissue.

O. T. SCHULTZ.

ENDOTHELIOMA OF THE PALPEBRAL CONJUNCTIVA. K. STOJALOWSKI and J. STASIŃSKA, *Virchows Arch. f. path. Anat.* **286:70**, 1932.

The authors present a brief description of a primary endothelioma of the palpebral conjunctiva in a youth aged 20. Endothelioma of the conjunctiva is rare.

O. T. SCHULTZ.

PRIMARY LYMPHOSARCOMA OF THE THYROID GLAND. C. O. RICE, Virchows Arch. f. path. Anat. **286**:457, 1932.

Rice, of Minneapolis, describes five primary lymphosarcomas of the thyroid gland, encountered in the surgical pathologic material in Wegelin's pathologic institute at Bern in the years from 1922 to 1929. The patients were women aged 50, 62, 67, 69 and 80, respectively. The tumor arises from the lymphoid follicles that are not infrequently seen in the thyroid gland.

O. T. SCHULTZ.

RETICULOSARCOMATOSIS. E. BENECKE, Virchows Arch. f. path. Anat. **286**:693, 1932.

The onset of illness in a boy, aged $4\frac{1}{2}$ years, was insidious, with recurrent colicky pains in the upper part of the abdomen. A tumor could be felt in this region. The course of the illness was afebrile. The blood picture was unaltered except for moderate secondary anemia. Biopsy of the abdominal tumor left the clinical diagnosis undetermined as between diffuse reticulo-endotheliosis and primary localized reticulum cell sarcoma. Death occurred eight weeks after the onset of the illness. Autopsy revealed a large nodular tumor which arose from the retroperitoneal lymph nodes of the celiac region and which had invaded the pancreas, the left suprarenal gland and contiguous structures. The lymph nodes generally were enlarged, and in the neck the muscles were invaded by neoplastic tissue. There were multiple small nodules in the lungs and liver. The spleen was enlarged. The bone marrow was red and hyperplastic. Microscopically, the tissue of the main tumor, of the smaller tumor nodules and of the spleen, lymph nodes and bone marrow consisted of hyperplastic reticulum cells. Discussion is limited to the hyperplasias of the reticulo-endothelial system which may be grouped together under the term aleukemic reticulo-endotheliosis or reticulosis. In the majority of the reported cases the hyperplasia is secondary to septic infection. The neoplastic hyperplasias, the group in which Benecke's case belongs, may be diffuse and involve the entire reticulo-endothelial system, or they may occur as localized tumor formations with multiple metastases. In Benecke's case the gross anatomic picture was that of a large invasive tumor apparently with metastasis. Histologically, however, the picture was that of a disease of the entire reticulo-endothelial system. Direct transformation of Kupffer's cells to tumor cells was evident in the liver, and of reticulo-endothelial cells to tumor cells in the lymph nodes, spleen and bone marrow.

O. T. SCHULTZ.

RETICULUM CELL SARCOMA OF LYMPHOID TISSUE. F. ROULET, Virchows Arch. f. path. Anat. **286**:702, 1932.

In a previous issue of *Virchow's Archiv für pathologische Anatomie und Physiologie und für klinische Medizin* (**277**:15, 1930) Roulet proposed the name retothelium for those cellular elements of the reticulo-endothelial system that lie directly on the reticulum of lymphoid tissues. Tumors derived from such cells he termed retothelial sarcomas, and claimed for them a relatively low grade of malignancy. In the present communication he describes eight cases of reticulum cell hyperplasia, some of which were more highly malignant than the previously described tumors, the latter being represented in the present series by two reticulum cell sarcomas of the axillary lymph nodes. The more highly malignant tumors had their origin in the tonsils or in pharyngeal lymphoid tissue. The series includes one case of diffuse, aleukemic, non-neoplastic hyperplasia of the reticulo-endothelial system and two cases in which there was diffuse hyperplasia as well as invasive neoplastic tumors with metastasis, the latter illustrating the transition from retotheliosis to retothelial sarcoma and retothelial sarcomatosis. One case of reticulum cell sarcoma is described, in which four years before death the blood picture was that of lymphatic leukemia. Under roentgen therapy the blood picture became normal, but there developed a mediastinal tumor of the character of a reticulum cell sarcoma, together with hyperplasia of the reticulum

cells of other lymph nodes. This case suggests the possibility of reversion of lymphoblastic tissue to the more primitive reticulum cell tissue. The author believes that it is necessary to separate the neoplastic and the non-neoplastic hyperplasias of reticulum cells from the neoplastic and the non-neoplastic hyperplasias of endothelial cells.

O. T. SCHULTZ.

Medicolegal Pathology

SUDDEN DEATH. T. H. B. BEDFORD, *J. Path. & Bact.* **36**:333, 1933.

One hundred and ninety-eight persons were found by the receiving officer to be dead on arrival at the hospital during twenty-one years, from 1910 to 1930. The relative importance of the various organs involved and the nature of the actual lesions have been investigated. The chief causes of death found were: disease of the coronary arteries, 80 cases; valvular disease of the heart, 35 cases; aneurysm of the aorta, 22 cases; disease of the respiratory organs, 19 cases, and cerebral hemorrhage, 15 cases; the coronary arteries were found diseased in 104 cases. In 15 cases postmortem examination failed to reveal any lesion which might have accounted for death. Attention has been drawn to the steady increase in the number of cases during the period covered by the review, and figures are presented which suggest that this increase is a general one, affecting to an equal degree the incidence of sudden death from all causes.

AUTHOR'S SUMMARY.

ARSENIC CONTENT OF THE ASHES OF HUMAN CADAVERS. H. JESSER and A. SCHREMPF, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **20**:278, 1933.

The quantitative method of Ramberg (*Ztschr. f. Untersuch. d. Lebensmitt.* **52**: 448, 1926) for the determination of arsenic gives excellent results. In the ashes of a person who was treated with arsphenamine during his lifetime, the quantity of arsenic found was about the same as in ordinary cases of lethal arsenic poisoning. If a corpse which contained arsenic, either on account of arsenical medication or because of arsenical poisoning, was cremated, and subsequently an arsenic-free body was cremated in the same place, arsenic was found in the ashes of the latter. It was observed that the ashes of nine otherwise arsenic-free bodies cremated in succession showed the presence of arsenic, if an arsenic-containing body was first cremated in the same crematorium. These findings are of momentous medicolegal significance and should prevent erroneous interpretations.

E. L. MILOSLAVICH.

SUICIDE FOR INSURANCE PLANNED TO APPEAR AS A MURDER. A. MERKEL, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **20**:332, 1933.

A man was found shot dead in a wood under conditions indicating robbery and murder. However, from the position of the ejected shell and from a bullet scar on a nearby tree, it was decided that the man had committed suicide, holding the revolver in a peculiar position back of his occiput. The motive was economic distress and desire to provide for his family with the insurance money.

JACOB KLEIN.

MEDICOLEGAL ASPECTS OF DEATH FROM HEMATOPERICARDIUM WITH SPECIAL REFERENCE TO CARDIAC RUPTURE. B. LEWIN, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **21**:34, 1933.

In this thorough review of sudden death from hemato-pericardium, the author discusses the etiology, clinical manifestations and pathologic anatomy from the medicolegal point of view. Blood may enter the pericardium from rupture of the cardiac muscle, from a torn coronary vessel or from rupture of that part of the aorta within the pericardium. There is no case recorded in which fright or other emotional shock caused rupture in a normal heart. Cardiac rupture may be spontaneous or traumatic in origin. In the former instance the most common lesions are embolism, sclerosis or thrombosis of the coronary vessels, abscess of the

myocardium, brown atrophy, tuberculosis, syphilis and tumors. Traumatic rupture may be due to injury of the thorax sustained in boxing, falling from a height, crushing injuries, a kick by a horse and similar accidents. There may be such varied symptoms as severe precordial pain radiating to the left arm, cyanosis, restlessness, collapse, exhaustion and vomiting. From a medicolegal standpoint it is important to obtain a thorough history of the trauma with relation to the onset and course of the symptoms. It is essential to know whether or not the patient was ill before the trauma. Numerous clinical experiences and experiences at autopsy are briefly presented. The suggestion is made that surgical intervention may save the life of the patient in some instances. There is a comprehensive bibliography on this subject.

JACOB KLEIN.

INTRAVENOUS INJECTION OF METALLIC MERCURY. R. HEY, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **21**:257, 1933.

A 35 year old woman injected 2 cc. of metallic mercury into the cubital vein in an attempt at suicide. On the fourth day she suffered from diarrhea, palpitation and stomatitis. In the course of several weeks there was complete recovery from all symptoms. Seven years later the patient died of tuberculosis, in no way related to the mercurial intoxication. Anatomic study demonstrated metallic mercury in the liver cells, lungs and kidneys. No mercury was found in the central nervous system, pancreas, suprarenals, uterus or ovaries.

JACOB KLEIN.

DEATH WHILE BATHING IN COLD WATER. 1. RUDOLF KLOTZ, München. *med. Wchnschr.* **79**:1690, 1932. 2. KARL EISELBERG, München. *med. Wchnschr.* **79**:1691, 1932. 3. GRASSL, München. *med. Wchnschr.* **79**:1469, 1932. 4. J. P. ZUM BUSCH, *Deutsche med. Wchnschr.* **159**:15, 1933.

1. The sudden cooling of the surface of the body may be an important factor in causing death by drowning. This cooling causes a shift in the blood from the surface of the skin to the hypogastric and splanchnic region. The resulting dilatation of the visceral capillaries causes vertigo, weakness and collapse. Deaths from bathing in cold water during hot weather may be due to paralysis of the splanchnic capillaries from sudden cooling of the surface.

2. Unpleasant manifestations while bathing in cold water are often allergic reactions. In sensitive persons a cold bath may induce vertigo, weakness and even death by asphyxia.

3. The author himself noticed a sudden coldness in the feet while swimming in cold water on a hot day. On rubbing the cold areas large wheals formed. He felt ill, became faint and fell unconscious. After several minutes he recovered. A healthy, 50 year old woman, while bathing, had malaise, vomiting and vertigo. She might have drowned had not a bystander pulled her out. Her legs swelled from the ankles to the upper third of the thigh and were painful. A similar neuromuscular disturbance may cause "goose-flesh" and headaches after bathing. In more serious cases even death may result.

4. Some deaths during bathing may be due to allergy to cold. The author, although he has bathed in cold water since childhood, was sensitive to cold and suffered from paroxysmal sneezing and rhinorrhea. He could induce such an attack by sticking his foot out of the warm bed. In cold water his hands became swollen, red and itchy. On several occasions he experienced sudden weakness while swimming, so that he reached shore with the greatest difficulty and then collapsed. There would then be an eruption of giant urticaria about the joints. A similar reaction occurred once in a cold air bath. Such hypersensitiveness may occur only at times. Now, at the age of 65, the author swims in cold water without harmful symptoms. He considers the condition a form of allergy to cold.

JACOB KLEIN.

SPONTANEOUS RUPTURE OF THE AORTA. K. WOLFF, *Virchows Arch. f. path. Anat.* **289**:1, 1933.

The histologic examination of six examples of so-called spontaneous rupture of the aorta confirmed the observations of Erdheim and others that rupture occurs through severely damaged areas of the media. In such areas, which appear as bands or streaks in sections, the media is degenerated, structureless and devoid of nuclei. Masses of mucoid material are seen in the degenerated areas. Similar lesions were seen in the aorta at points distant from the rupture, in the pulmonary artery, and in the carotid, iliac and femoral arteries, leading Wolff to suggest that the process is a systemic disease of the arteries, the first manifestation of which is focal destruction of the elastic tissue. The degenerative lesions begin about the vasa vasorum, hence Wolff postulates a noxious agent, probably chemical in nature, that reaches the arterial wall by way of the nutrient vessels. Increased blood pressure is an added factor in the production of the lesions and in the rupture. In one case the degenerative process of the media of the aorta had led to marked proliferation of a type that Wolff terms re-formation of the wall, since connective and elastic tissue and smooth muscle all took part in the proliferative process. The article ends with a tabulation of nineteen cases of spontaneous rupture of the aorta, including thirteen previously reported cases and Wolff's six.

O. T. SCHULTZ.

NECROSIS AND HEMORRHAGE IN TUMORS OF THE BRAIN. B. KARITZKY, *Virchows Arch. f. path. Anat.* **289**:83, 1933.

A medicolegal case raised the question whether the necrosis and hemorrhage noted in a tumor of the brain were the result of an electric shock that the victim had sustained. To furnish information for the solution of this question, the author examined 115 gliomas and 18 ganglioneuromas of the brain, the material having been collected since 1912 in Schridde's pathologic and medicolegal institute at Dortmund. Macroscopically evident necrosis was noted in 80 per cent of the tumors, and hemorrhage in 76 per cent. Necrosis is the result of the cellular character of the tumors and is brought about by degenerative changes in the vessels of the tumor; necrosis was not observed in denser, acellular tumors. Hemorrhage is secondary to necrosis. In only one of the tumors examined had there been fatal hemorrhage without necrosis, due to external action.

O. T. SCHULTZ.

Society Transactions

INTERNATIONAL ASSOCIATION OF MEDICAL MUSEUMS, AMERICAN AND CANADIAN SECTION

Twenty-Sixth Annual Meeting, Washington, D. C., May 8, 1933

GEORGE R. CALLENDER, *Fort Sam Houston, Texas, President, in the Chair*

THE MUSEUM OF PATHOLOGY OF THE UNIVERSITY OF TORONTO. Presented by
T. H. BELT.

This museum has been developed for teaching purposes alone and has been arranged somewhat differently from museums in general in that the total collection, which comprises about three thousand mounted specimens, is divided into ten groups, each of which is housed in a separate room. One of these rooms is devoted to the teaching of general pathology, and the other nine to specimens illustrating the various aspects of special pathology.

A NEW FORM OF MUSEUM CATALOG. WILLIAM BOYD, Winnipeg, Canada.

A method was described which has proved to be a satisfactory solution of the cataloging problem. This is primarily a teaching collection of about fifteen hundred specimens extensively used by students of pathology for reading purposes. The specimens are mounted under watch-glass and are placed in three tiers on either side of a home-made fixture similar to a magazine desk in a library, which replaces the ordinary museum case. The distinctive feature is that along the entire length of the fixture and attached to the lowest tier there runs a thin board, 11 cm. in depth, which is set 8 mm. from the stand; this provides a narrow box which is divided by transverse partitions corresponding in size with the largest of the watch-glass specimens. This holds a stout card 5 by 7 inches on which can be typed the description of the specimen (gross and microscopic), summary of the clinical history and observations at autopsy. Both sides of the card are used, and more than one card may be employed, carrying, if desired, a photomicrograph and reduced roentgenogram on the back. Three of these cards are contained in each receptacle, corresponding to the three specimens immediately above on the stand. The specimens are not labeled, but each carries the number of its corresponding card, thus stimulating the student to make his own diagnosis. Each fixture consists of a 12 foot stand carrying eighty-four specimens, and under this arrangement from thirty to forty students can work with comfort at one time without interruption.

THE SELECTION OF A LIBRARY OF PATHOLOGY. ROBERT A. MOORE, Cleveland.

The abstracts in five volumes each of the *ARCHIVES OF PATHOLOGY* and the *Centralblatt für allgemeine Pathologie und pathologische Anatomie* were indexed on the assumption that the journal most frequently abstracted is the most valuable journal. Twenty-two journals carried 50 per cent of the articles abstracted in these ten volumes. The remaining 50 per cent appeared in over two hundred journals. Journals of pathology carried 41 per cent of the literature, journals of other medical specialties 48 per cent and other journals and transactions 11 per cent. The cost per page showed that the German journals average 3.5 cents a page as compared with about 1 cent a page or less for the English, French and American journals.

DISCUSSION

GEORGE R. CALLENDER: It is gratifying that the comparative expense of the available literature has been presented in concrete form.

VICTOR C. JACOBSEN: Such an investigation is extremely helpful, especially during these times of financial stringency and practically universal reduction of budgets. The situation is especially acute in regard to German publications, the high price of which has become a serious matter. A closer collaboration between the work of the anatomic and pathologic departments is also needed on both economic and scientific grounds.

A PROCESS OF EMBALMING, AND SOME NOTES ON DIDACTIC ANATOMIC TECHNOLOGY. PEDRO ARA, Professor of Systematic Anatomy, Madrid, Spain.

The speaker, who had come from Spain especially for the purpose of attending this meeting, presented a truly remarkable specimen consisting of the upper half of the thorax and head of an old monk, preserved without any shrinkage to such a high degree of perfection that the physiognomy and even the expression were retained in an extraordinary lifelike manner. The technic followed was essentially a simple process of paraffinization similar to that used in the impregnation of material for histologic purposes; therefore a good preliminary fixation, absolute dehydration, etc., formed the basis of the method employed.

1. IMPROVED TECHNIC IN THE MAKING OF GLASS FRAMES FOR MOUNTING SPECIMENS IN CORRECT ANATOMIC POSITION. 2. THE DRY MOUNTING OF CALCULI. 3. A HANDY MICROSCOPE LIGHT. JOSEPH GIROUX, Montreal, Canada.

1. Special devices in the making of glass frames to secure greater solidity by means of additional supports of the frame and to obtain greater facility in workmanship with the blowpipe and otherwise are described. 2. Calculi are best preserved when they are placed in a dilute solution of formaldehyde (1:10), washed in running water for twenty-four hours, passed through 98 per cent alcohol to restore their color, and finally, when perfectly dry, painted with a hard photographic varnish. Sectioning, when required, is done under water by means of a small jeweller's saw-blade with very fine teeth on both edges, the cut surface being polished on a piece of glass covered with fine emery powder and water. 3. An efficient microscope lamp may be made from a 4 pound potassium acetate tin with a hole cut in one side to expose a 500 cc. flask of distilled water fastened within, and supplied with an electric light bulb, two mirrors suitably adjusted for reflection and ventilation slits.

METHODS OF MOUNTING GROSS SPECIMENS OF EYES AT THE ARMY MEDICAL MUSEUM. HELENOR CAMPBELL WILDER, Washington, D. C.

Specimens fixed in Kaiserling's solution are mounted on sheet celluloid with a solution of celluloid in acetone. Celloidin blocks, from which sections have been cut, are partially dehydrated in 95 per cent alcohol, stuck to the faces of small museum jars with thin celloidin and mounted in equal parts of absolute alcohol and cedar oil. Both types of mounts are sealed with Duco household cement.

A SIMPLIFIED GELATIN METHOD FOR MOUNTING MUSEUM SPECIMENS. N. S. SAHASRABUDHE, Nagpur, India.

Preliminary fixation is carried out by injection of a dilute solution of formaldehyde (1:20) into the carotid or femoral artery. Sections taken are preserved in a modified Jore's solution, and the gelatin (French, gold label) is mixed with water in the proportion of 1:10, 50 cc. of a solution of formaldehyde being added thereafter to every 500 cc. of the gelatin mass. For mounting, the jar is held on the slant and the specimen arranged on one surface; liquid gelatin is then introduced

to cover it and is allowed to congeal, the jar being placed within an ice jacket for five minutes for this purpose. After it is solidified, the remaining space in the jar is filled with a dilute solution of formaldehyde in distilled water and sealed.

CURRENT ACTIVITIES AT THE ARMY MEDICAL MUSEUM. VIRGIL H. CORNELL, Washington, D. C.

These include studies of the functioning of the bladder and the eye, lymphatic tumor registries, the work done by the museum as the central laboratory of pathology for the army, the development of three-color photography, rearrangement of exhibits and improvement of lighting in the museum, various exhibits presented during the past year by the museum and the file of results of original research.

DISCUSSION

V. C. JACOBSEN: The Army Medical Museum has done excellent work in assembling material in its tumor and other registries. From time to time there arise problems in pathology promulgated by some person which require a great deal more investigation to evaluate properly. Thus the work being done by Cushing on changes in the hypophysis may revolutionize the pathology of eclampsia. I consider it essential to examine the hypophysis carefully in all cases of eclampsia. No one person will obtain much material of this kind, so that it is important to assemble the specimens at one point. I am wondering whether the Army Medical Museum might at some time attempt to collect such hypophyses. I do not know any better place.

HOWARD T. KARSNER: It seems to me that a paper of this sort should not go by without adequate discussion. It represents what can be done by the United States Army Medical Corps in the face of the most distressing conditions. I think that as an association we should feel a great sense of pride in its accomplishments. As Dr. Jacobsen has said, many things might be utilized in the way of research. The state of New York has been trying to determine the standards of surgical pathologists, and examinations are being conducted which are of the utmost value. It is interesting to know the results of this activity; the subject may at some time reach national proportions. It is to be hoped that the United States will be able to maintain the high standards of the Army Medical Corps.

GEORGE R. CALLENDER: The Army Medical Museum is the national medical museum, and the pathologists of this country have been of assistance. In the line of surgical research we have housed the material of a great many investigators, consisting of reprints, slides and many specimens. Every year more and more is added to this wealth of material. I should like to remind the members that the Department for the Preservation of Objective Results of Medical Research is essentially a part of the International Association of Medical Museums, the material being housed at the Army Medical Museum by permission of the Surgeon-General in response to the request of the council of this association and as a result of its organization.

AN INEXPENSIVE METHOD OF DEMONSTRATING HISTOLOGIC SLIDES TO SMALL GROUPS. WALLACE J. PLUMPTON, Montreal, Canada.

A simple apparatus was demonstrated which is quickly set up by placing a microscope in front of an ordinary lantern slide projector and removing the eye piece of the microscope.

SANTALIN, A SELECTIVE STAIN FOR THE FATTY ACID CRYSTALS IN FAT NECROSIS. W. F. SHERIDAN, Washington, D. C.

A SIMPLE KNIFE SHARPENER. WILLIAM BOYD, Winnipeg, Canada.

A knife sharpener, similar in principle to the Schmidt microtome knife sharpener, can easily be made by the hospital mechanic at a trifling cost. It consists of a knife carrier which slides on ball bearings on a base of plate glass, the knife moving on a smaller plate of ground glass. Abrasives are poured over the latter, the most useful being fine emery and white rouge. With this simple device a microtome knife can be given a perfect edge by any technician.

A SIMPLE SILVER TECHNIC FOR NERVES AND TACTILE CORPUSCLES IN PIGMENTED MOLES. GEORGE F. LAIDLAW, New York.

Nerve fibers in pigmented moles were shown by a rapid and simple silver stain based on that of Gross and Bielschowsky. Some nerves terminate in tiny bulbs on the nevus cells as they do on the tactile cells of the epidermis and the hair follicles. Other nerves have thick sheathing of Schwann cells. The stain confirms Masson's assertion that pigmented moles are neuromas and schwannomas of the sensory nerves of the skin.

A CASE OF HEMORRHAGE FROM THE NIPPLE DUE TO A BENIGN INTRADUCTAL POLYP. HELEN INGLEBY, Philadelphia.

A married woman, aged 32, had a brownish watery discharge from the nipple two years before operation. One year later a tumor was noticed, and six weeks before admission to the hospital she had bleeding from the nipple, lasting for ten days. A benign intraductal polyp was found which had the structure of a fibroadenoma. The ducts in the adenoma resembled those of the surrounding breast and were in the late premenstrual phase. The mechanism of formation of this type of tumor was discussed.

A CASE OF PRIMARY CALCIFICATION IN MUSCLE FIBERS OF THE HEART. DORA DENG, Shanghai, China.

A white woman, aged 28, died of chronic glomerular nephritis. At autopsy numerous calcified plaques were found in all systemic arteries and three small calcified nodules in the wall of the left ventricle. On the basis of Rabi's experiment and Wells' and Kuttner's hypothesis, the extensive deposits of calcium were explained as due to phosphoric acid retention resulting from renal lesions and to the concentration of carbon dioxide in the blood at those particular sites.

AORTIC STENOSIS: A DIFFERENTIAL STUDY IN CALCIFIED BICUSPID VALVES BETWEEN THOSE OF CONGENITAL OR INFLAMMATORY ORIGIN. LOUIS F. BISHOP, New York, and MAX TRUBEK.

With fusion and calcification of the aortic cusps it was often difficult to decide on gross examination whether we were dealing with an old inflammatory process or with a congenitally bicuspid valve with subsequent calcification. By the method described by Lewis and Grant (1923), serial sections stained for elastic and connective tissue were cut through the ridge or raphe dividing the conjoint cusp. A normal valve and a typical congenital raphe were similarly sectioned for comparison with the pathologic material. The method proved a satisfactory aid in most of the cases.

DISCUSSION

M. E. ABBOTT: This is a very valuable contribution. Lewis and Grant first established a differential microscopic picture of the congenital as compared with the acquired lesion, but stated that additional studies on the architecture of bicuspid aortic valves were desirable in order to verify their conclusions, which were necessarily drawn from a relatively small number of cases. Dr. Bishop has done this and has also delineated the histologic features of the two types of cases clearly.

CONGENITAL ANEURYSM OF THE INTERVENTRICULAR SEPTUM. ERIC MASSIG, Toronto, Canada.

This case was of a man, 49 years of age, who died of coronary disease. An unrelated finding at autopsy was a small aneurysm of the membranous portion of the interventricular septum. It extended from the left ventricular cavity into the medial leaflet of the tricuspid valve. There were no signs of acute or chronic inflammatory changes about the aneurysm.

DISCUSSION

ROBERT A. MOORE: Are there any criteria by which differentiation of a congenital origin can be made?

T. H. BELT: The absence of any sign of endocarditis is in favor of an anomaly.

M. E. ABBOTT: The seat of the aneurysm in this case is characteristic of a congenital lesion.

CONGENITAL ANOMALIES OF THE CORONARY ARTERIES: REPORT OF AN UNUSUAL CASE ASSOCIATED WITH CARDIAC HYPERTROPHY. EDWARD F. BLAND, PAUL D. WHITE and JOSEPH GARLAND, Boston.

In a boy dying at the age of 3 months, abnormal origin of the left coronary artery from the pulmonary artery was found associated with marked enlargement of the heart (due to hypertrophy and dilatation of the left ventricle), together with extensive degenerative changes in the ventricular wall supplied by the malposed vessel. In view of these findings, it is probable that the paroxysmal attacks of acute discomfort precipitated by exertion and associated with profound vasomotor collapse occurring in this infant were angina pectoris. The electrocardiographic picture was similar to that seen in adults with serious coronary disease. In the few recorded cases (eight in addition to our own) of this rare anomaly a characteristic pathologic picture has resulted. Death within the first year has been the rule. Two of the cases have been exceptional.

DISCUSSION

V. C. JACOBSEN: This work is particularly valuable in that it shows how the heart reacts to what is essentially occlusion of one main coronary artery. Some nourishment from a venous supply is possible, and to a certain extent this has occurred in this case. Coronary arteriosclerosis in older patients has been cited, with no particular change in the myocardium and without the history of a definite cardiac attack even in the presence of marked narrowing of the coronary vessels. In such cases the myocardium must have been nourished by other vessels such as the thebesian vein. No hard and fast rule can be laid down as to what to expect when one coronary artery (and not both) is occluded.

M. E. ABBOTT: Dr. White's presentation of the clinicopathologic findings is valuable. This is the first case of anomalous origin of the left coronary from the pulmonary artery in which an electrocardiogram has been taken, linking up the changes that must have occurred in the myocardium with the resultant functional disturbance.

P. D. WHITE: Electrocardiograms have been taken in two cases of idiopathic hypertrophy of the heart in infancy.

NEW YORK PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, May 26, 1933*PAUL KLEMPERER, *President, in the Chair*

MULTIPLE SACCULAR ANEURYSMS OF THE CEREBRAL ARTERIES: RUPTURE INTO THE SUBDURAL SPACE. MILTON HELPERN.

A 51 year old white laborer was found dead in bed. Because of a recent injury to the hand and to the forehead the cause of death was investigated by the medical examiner's office. At autopsy, the body was poorly nourished. Except for a large fatty liver and an inelastic but smooth aorta, the organs were not unusual. The skull was uninjured.

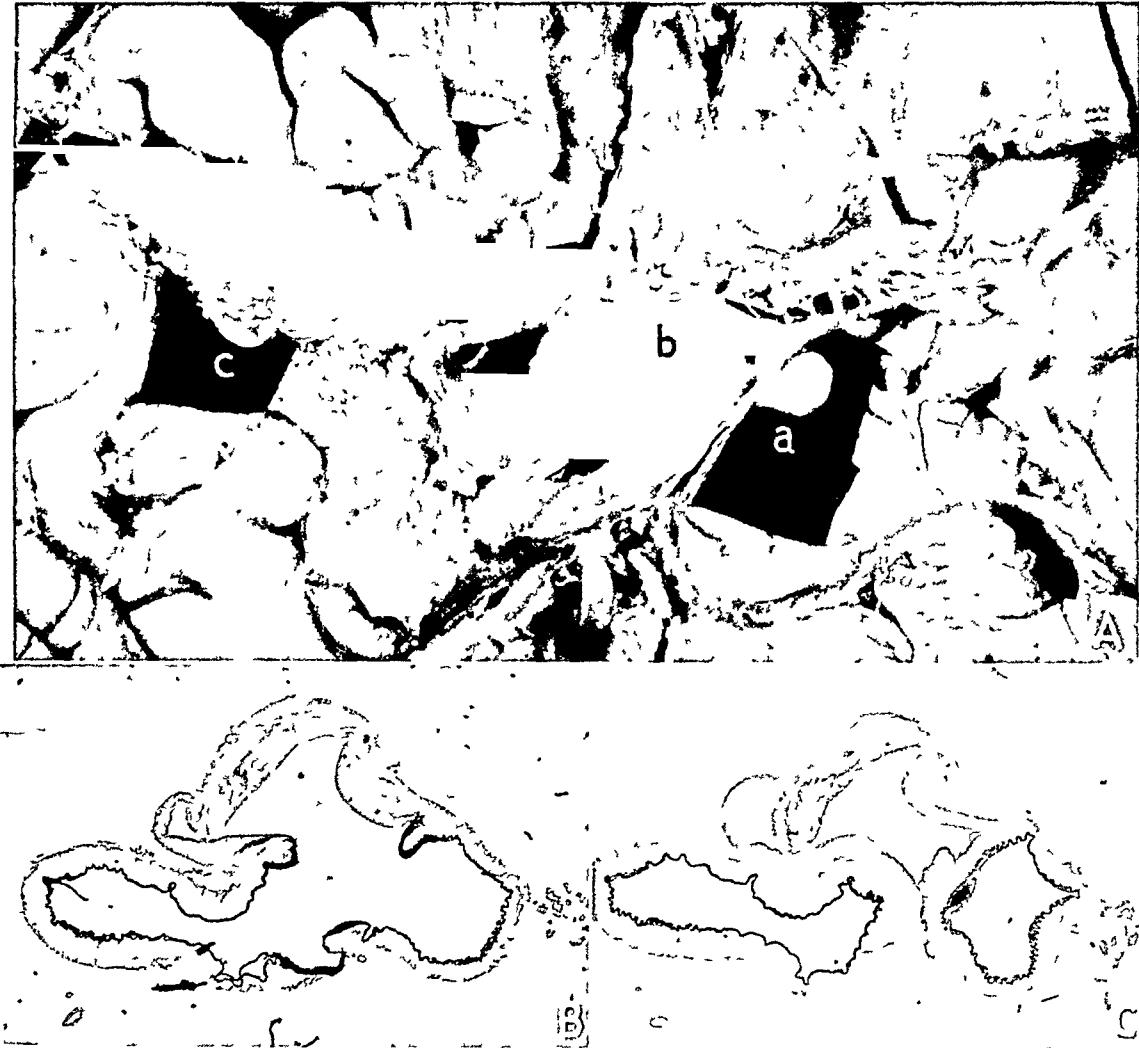
A large, fresh, subdural hemorrhage weighing more than 85 Gm. covered the base of the skull and extended upward over both cerebral hemispheres. The blood was not adherent to the surface of the arachnoid or to the smooth inner surface of the dura. The communicating veins between the pia and the dural sinuses were not torn, and the surface of the brain was intact. A small, thin area of sub-arachnoid hemorrhage localized over the antero-inferior portion of the left temporal lobe was continuous in the fissure of Sylvius with a small collection of soft, clotted blood overlying a saccular aneurysm 6 mm. in diameter which arose from the superior and lateral wall of the commencement of the left middle cerebral artery just beyond the origin of the posterior communicating branch (fig., *a*). The aneurysm was situated above and lateral to the internal carotid artery at the point where that vessel passes out of the subdural space into the subarachnoid space to continue as the middle cerebral artery. When the brain was removed, the carotid stump was cut close to the circle of Willis, probably through the site of the rupture of the aneurysm, which was not found elsewhere. The rupture at the point of transition from the internal carotid to the middle cerebral artery explained the large subdural hemorrhage and only slight localized subarachnoid hemorrhage.

Two additional saccular aneurysms were found arising from the cerebral arteries. Halfway along the left anterior cerebral artery, the vessel bifurcated into two closely placed parallel branches of slightly unequal caliber which reunited in the region of the anterior communicating branch. The second aneurysm, 1.5 mm. in diameter, arose at the point of bifurcation and was wedged between the two branches, its inferior surface bulging as a small translucent nodule (fig., *b*). The third aneurysm was in the angle of the first bifurcation of the right middle cerebral artery (fig., *c*). In size and structure it was similar to the first aneurysm described. The basilar and carotid arteries were slightly thickened. No lesions were found in the brain substance, which on chemical examination contained a moderate amount of ethyl alcohol.

The large aneurysm on the left middle cerebral artery and the small one on the left anterior communicating artery were sectioned for histologic examination. Both occurred at a bifurcation; the former, where the internal carotid became the middle cerebral artery after giving off the posterior communicating branch, and the latter, at the unusual bifurcation of the anterior cerebral artery in the middle of its course. Weigert's elastic tissue stain and van Gieson's stain revealed an aneurysmal wall almost devoid of internal elastica and muscularis and composed of a slightly thickened continuation of incomplete intima and adventitia. The wall of the larger aneurysm was considerably thinner than that of the smaller one on the anterior cerebral artery, which is shown in the figure, *B* representing the origin at the point of bifurcation and *C*, a few sections anteriorly, representing the aneurysm wedged between the two branches. The almost complete disappearance of internal elastica in the aneurysm is easily made out.

The aneurysms were saccular and obviously not due to arteriosclerosis, trauma, syphilis or other inflammation. Their occurrence at the bifurcation of the cerebral

arteries and their multiplicity, size and histologic structure place them in the group described by Forbus (Miliary Aneurysms of the Cerebral Arteries, *Bull. Johns Hopkins Hosp.* 47:239, 1930). He expressed the belief that the lesions are acquired, arising from a combination of focal weakness in the vessel wall, as a result of a congenital defect in the muscularis at points of bifurcation, and subsequent degeneration of the internal elastica due to continued overstretching by the force of blood pressure. Rupture of cerebral aneurysms into the subdural space with an absence of massive subarachnoid hemorrhage is unusual, in this instance



A, the base of the brain. Multiple saccular aneurysms are seen at a, b and c, arising at points of bifurcation of the cerebral arteries. The temporal lobes have been removed. There is no subarachnoid hemorrhage. Black paper has been inserted behind the vessels for contrast. B and C, sections through the left anterior cerebral artery at the site of the aneurysm seen in A at b; Weigert's elastica stain. B shows the aneurysm devoid of elastica and muscularis, arising at the bifurcation; C, the aneurysm a few sections farther on, wedged between the two branches.

probably occurring at the point where the internal carotid artery emerged from the subdural into the subarachnoid space to continue as the left middle cerebral artery. In a clinical case of this type, the diagnosis would be obscured by the

obtaining of a clear spinal fluid on lumbar puncture instead of the usual bloody type. These aneurysms, judging from their size, should not be designated as miliary.

METASTATIC CARCINOMA OF THE SPLEEN. ELMA BARANY and ANGELO M. SALA.

As metastatic carcinoma of the spleen is rare, the two cases presented here are of interest.

CASE 1.—A woman, aged 68, was admitted to the New York City Cancer Institute Hospital on Sept. 19, 1932, with pain in the abdomen of four months' duration. There were a firm mass in the right axilla, a few subcutaneous nodules around the umbilicus and a fixed, hard mass in the pelvis, pushing the uterus to the left. A clinical diagnosis of carcinoma of the ovaries with metastases to the umbilicus and right axilla was made. The patient died on December 27. Autopsy confirmed the diagnosis of carcinoma of the ovaries with general carcinomatosis. There were metastases to the liver and to the spleen, which presented a metastatic deposit in its parenchyma, about 1 cm. in diameter, extending nearly to the surface. Histologically, both ovaries and all the metastatic deposits showed adenocarcinoma.

CASE 2.—A man, aged 72, was admitted to the New York City Cancer Institute Hospital on Aug. 8, 1932. Prostatectomy had been performed in 1931, and the prostate proved to be malignant. Physical examination showed nothing of importance except, on rectal examination, a nodular mass in the prostatic area. A diagnosis of carcinoma of the prostate was made, and high voltage roentgen treatment was administered. The patient died on Jan. 9, 1933. Postmortem examination on January 14 revealed enlarged tracheobronchial nodes in the area of the hilus of the right lung, which were matted together to form an encapsulated mass about 6 by 4 by 3 cm., giving the appearance of a neoplasm. The spleen weighed 400 Gm. At its lower pole there was a well demarcated mass about 8 cm. in diameter, replacing about two thirds of the parenchyma. A recurrent mass was found in the prostatic area, and all the retroperitoneal nodes were neoplastic. The histologic picture of the recurrence, as well as of the lymph nodes and the splenic metastases, was that of a diffusely growing, small cell, poorly differentiated carcinoma.

It is difficult to understand what makes the spleen so unfavorable for secondary carcinoma when its structure and function closely resemble those of lymph nodes, which are favorite sites of carcinomatous deposits. Some writers explain this by the fact that the spleen does not possess any specific parenchymatous cells; some find the reason for it in the pulsation of the organ, which would make it difficult for the tumor emboli to attach themselves; some mention the sharp angle of the splenic artery, which would keep out the metastatic emboli, and some refer to the immunologic resistance of the spleen, by which it would destroy the malignant cells if they were able to get there. That the splenic parenchyma itself is devoid of lymphatics may be still another explanation. The main reason, however, may lie in the fact that one does not look closely enough to find metastatic deposits, which at times may be minute. Until 1927, only a few cases had been described in the literature; since then, there have been an increasing number of reported cases of splenic metastasis. Krumbhaar described twenty-one metastatic carcinomas of the spleen. Yokohata, among twenty-nine unselected cases of carcinoma, was able to demonstrate metastases in ten, but they were all only of microscopic size and were situated mostly in vessels or sinuses. At this stage one can think of these collections only as emboli, the development of which into true metastatic growths is not necessarily taken for granted.

AN UNIDENTIFIED PARASITE IN THE CARDIAC MUSCLE. WILLIAM C. VON GLAHN.

A carpenter, aged 62, born in Virginia, first admitted to the hospital because of cardiac decompensation, was found to have aortic stenosis and insufficiency. At

the end of four weeks, compensation was sufficiently restored to permit his return home. He was readmitted with lobar pneumonia and died on the fourth day of his illness.

The aortic valve was extensively calcified; the heart was hypertrophied. There was consolidation of the lower and middle lobes of the right lung.

In the hypertrophied cardiac muscle the nuclei were often indented or invaginated, owing to the presence of peculiar bodies lying within the sarcoplasm. The end of the body near the nucleus was bluntly rounded; the other end was pointed. Near the bluntly rounded end was an oval vesicular nucleus containing particles of chromatin, and close to this nucleus in some instances was a solid round structure. One or more vacuoles were seen near the pointed end. The bodies measured 52.5 microns in length and 5.5 microns in width. They were usually straight, though in one instance one body was turned abruptly at right angles close to the nucleus and another was sharply bent on itself.

Two larger bodies were found which had been cut across in sectioning. One of these fragments measured 63 microns in length and 7 microns in width. Near the rounded end was a huge nucleus, 5.8 microns wide, in which were three nucleoli, the largest measuring 3.8 microns in diameter. The nucleus was constricted at its midportion as though in process of division. The other fragment, 45.5 microns long and 7 microns wide, likewise had a rounded end; its oval nucleus measured 10.5 by 4.5 microns. The single nucleolus was 2.4 microns in diameter.

Another of these bodies was divided longitudinally through part of its length so that it was roughly Y-shaped. There were two rounded ends directed toward the nucleus; the other end was sharply pointed. Close to one of the rounded ends were two nuclei; in the other was a single nucleus. In many muscle fibers fragments were found, and it was apparent that they often represented more than one of these bodies.

Staining Reactions of Bodies

Stain	Reaction
Hematoxylin-eosin	Eosinophilic
Gram	Gram-positive
Mallory's phosphotungstic acid hematoxylin	Yellow
Iron hematoxylin	Black
Carbol fuchsin followed by 1 per cent acid alcohol	Not acid-fast
Giemsa	Nucleus deep blue; remainder, robin's egg blue
Eosin; methylthionine chloride, U. S. P. (methylene blue); azure B	Nucleus very deep blue; remainder, dark blue

The only internal structure that could be distinguished in the bodies, aside from vacuoles and the nucleus with its nucleolus and chromatin material, was fine granules, usually in the blunt round portion. In the phosphotungstic acid hematoxylin preparations, the periphery of the bodies was refractive.

The bodies were not encapsulated; they seemed somewhat rigid. They were situated always adjacent to the nucleus of the muscle, and the long axis was always parallel to the direction of the myofibrils. They appeared to be surrounded by clear fluid. The myofibrils were pushed to either side by the bodies, but otherwise were unchanged. The cardiac muscle containing the bodies was not appreciably enlarged as compared to the adjacent muscle. There was no inflammatory reaction. The bodies were especially numerous in the posterior part of the left ventricle and were less frequently observed in the muscle from the apex of this ventricle. None could be found elsewhere in the heart.

The only other voluntary muscle available for histologic study was the diaphragm, and this did not contain any of the bodies.

These bodies do not conform to any known form of degeneration; their definite shape and well preserved nuclei, together with their staining reactions, indicate that they are not simple degeneration products.

They do not conform to any hitherto described parasite known to lodge in the cardiac muscle or in other muscle.

Preparations have been shown to numerous persons, including protozoologists. The consensus is that the bodies are parasitic, but none could identify them.

MYXOMA OF THE TRICUSPID VALVE. THOMAS C. JALESKI (by invitation).

An obese Negro woman, 62 years of age, was admitted to St. Luke's Hospital because of failing vision in both eyes, and was found to have bilateral cataracts. There were no other complaints, nor were there any findings indicative of heart disease. Extraction of the cataract in the right eye was performed, and on the sixth postoperative day the patient suddenly collapsed, with a clinical picture of circulatory failure, the blood pressure being 60 systolic and 40 diastolic, and the pulse very feeble. She became steadily worse and died the next day.

At autopsy the only noteworthy lesions were in the heart and the pericardial sac. There was about 100 cc. of cloudy fluid in the pericardial sac, and the pericardium was hemorrhagic. The heart weighed 325 Gm. None of the valves were thickened, and there was no evidence of endocarditis. On the anterior cusp of the tricuspid valve, situated in the middle of the valve and about 5 mm. from its free margin, was a small, spherical tumor measuring 6 mm. in diameter and projecting 4 mm. above the surface of the valve. It was attached to the valve by a short, wide pedicle. Its surface was finely nodular, and it had a translucent, gelatinous appearance.

Microscopically, the tumor was a myxoma, showing a definite pedicle and firm papilliform processes forming the major part of the growth. It had a complete endothelial covering. Stellate and spindle-shaped cells with long fibrillar processes were present in the papillae, and the presence of elastic fibers in the tumor was proved by Weigert's stain. Thionine and mucicarmine stained the tissue very faintly, possibly indicating the presence of mucin. Morphologically, the growth was therefore characteristic of true myxomas of the valve.

DISCUSSION

ALFRED PLAUT: May I rapidly show a tumor of the tricuspid valve which came into my hands two weeks ago? My associates and I performed an autopsy on a new-born infant who lived for one hour and died with signs of a disturbance in circulation. Examination gave negative results except for a large tumor arising from the tricuspid valve and obliterating the tricuspid ostium. The large distention of the right auricle is not easily demonstrable in the photograph; it was much more conspicuous in the specimen. The tumor has a broad base. In the photograph one can see the tricuspid ring, the normal musculature of the myocardium and the tumor, which I rightly or wrongly call an angiofibroma.

Another picture shows connective tissue in the tumor and a distinct endothelial lining. The same picture in another area shows peculiar large clear cells which I do not recognize. The unusual thing about this tumor is its size. It led to obstruction of the flow of blood at the tricuspid ostium, and I think that that caused death. Otherwise the child was normal; there was nothing in the skull to account for death directly after birth.

FOUR CASES OF THYMIC TUMORS (TWO WITH DISTANT METASTASES). ANGELO M. SALA and ELMA BARANY.

We have been fortunate in having an opportunity within a short time to study four tumors of the thymic region; three patients have come to autopsy, and the fourth is still under observation. The uncommon occurrence of these tumors may be judged from the fact that in a rich experience including nearly

seventeen thousand autopsies, Douglas Symmers was able to collect only twenty-five cases (*Ann. Surg.* 95:544, 1932).

CASE 1.—A white man, 53 years of age, was admitted to the hospital on Feb. 17, 1933. The previous November he noticed a change in his voice which he attributed to a cold. He was better in two weeks, but relapsed after a month, at which time a roentgenogram of the chest revealed the true state of affairs. Besides the condition in the chest, there was a hard, fixed mass in the left supraclavicular region, just behind the lower third of the sternocleidomastoid muscle. Biopsy on this mass showed a reticulum cell lymphosarcoma. At autopsy, on March 11, 1933, a tumor measuring 15 by 6 by 5 cm. was found in the region of the thymus; it extended upward to just below the thyroid cartilage and downward to below the origin of the great vessels, invading the pericardium. A nodule 3 by 1 cm. was found in the right auricle, apparently invading the cardiac muscle by extension of the original tumor through the pericardium. Two other small nodules were found in the substance of the left ventricle, and there were metastatic foci in the right kidney and spleen, as well as in the neck, as previously noted. The roots of the lungs were adherent to the tumor, but the lungs were not invaded.

CASE 2.—This case is presented through the courtesy of Dr. Douglas Symmers, who performed the autopsy a short time ago. A white man about three months before death began to complain of fulness in his head on bending over. One month later there was noticed a small lump in the left sternoclavicular region which caused discomfort on breathing. The lump was removed for biopsy, and the discomfort disappeared. Two weeks before this operation there was noted a slight, intermittent paresthesia of the areas of the right and left ulnar nerves. There was no cough, loss of weight or dysphagia. At autopsy there was found a tumor measuring 15 by 10 by 5 cm., occupying the entire anterior mediastinum. It was attached to the pericardium on the right side. It pushed aside and compressed the upper lobe of the right lung but was not adherent to it. On the left side it was adherent to the lung but did not infiltrate. The tumor as a whole appeared to be well encapsulated and did not invade the surrounding structures. Many of the nodes immediately adjacent to the neoplasm were enlarged and rather firm.

Histologically, the two tumors described were identical, both in hematoxylin and eosin and in silver preparations. They were both definite reticulum cell lymphosarcomas.

CASE 3.—A white man, aged 45, was admitted to the hospital on March 23, 1933. The chief complaints were cough, weakness and loss of weight of three months' duration. Six weeks before admission a mass in the left axilla was noted. Two weeks before admission hoarseness developed. Death occurred in a few weeks as a result of lobular pneumonia. At autopsy there was found in the region of the thymus a tumor measuring 6 by 3 by 2 cm., extending down on the pericardium, but not penetrating it. The nearby hilar nodes were markedly enlarged. There was also enlargement of the retroperitoneal and peripancreatic nodes, as well as metastatic deposits in both suprarenal glands. The histologic picture of the primary tumor and of the metastases was that of epithelioma. There were noted in many areas of the original tumor, as well as in the axillary mass, condensations of the epithelium suggesting definite attempts at the formation of Hassall's corpuscles.

CASE 4.—A 28 year old white woman was admitted to the hospital, on Feb. 9, 1933, complaining of intermittent paroxysmal attacks of cough for one year, with expectoration of whitish, occasionally thick phlegm which was never streaked with blood. For two months she had had generalized pruritus. There was enlargement of the lower cervical nodes on the left side, and a large, firm node was present in the right axilla. Roentgenograms of the chest showed a large mass in the midline in the region of the thymus. A biopsy specimen from one of the cervical nodes showed the typical picture of Hodgkin's disease. This case

is therefore presented as one of thymic Hodgkin's disease. The patient is still under observation and is receiving high voltage roentgen treatments.

DISCUSSION

NATHAN CHANDLER FOOT: The third case is of particular interest on account of its rather unusual features. I have had the good luck to collect about five of these malignant tumors of the thymus in the course of a number of years, and I find that they fall into three groups: The lymphoid group includes a reticulo-endothelial type and an indeterminate Hodgkin-like type. The epithelial group is characterized by the production of large pearl-like bodies which resemble and probably represent a part of Hassall's corpuscles. The third group combines the characteristics of the other two and shows a great many epithelial ducts such as were seen in the third case reported by Dr. Sala and Dr. Barany. I have been on the lookout for another case. These tumors are somewhat difficult to classify; in the case which I saw, the growth developed in a young child and had somewhat teratoid characteristics; part of it was lymphoid, and part of it was made up of epithelial ducts without marked production of Hassall's corpuscles.

I do not think that distant metastases are as common as Dr. Sala indicates. Most of these cases show a predominant tendency toward local extension and invade the glands about the pulmonary hilus and the pericardium without going much farther, working their way into the lung and not going outside. The cases reported here present an unusually high number of distant metastases. In one of my cases there was a very distant metastasis. The tumor was a lymphosarcoma of the thymus; the patient had all the symptoms of acute lymphoid leukemia with a typical blood picture, and the whole blood stream was flooded with these cells although no other productive foci were found except the lymphosarcoma of the thymus.

ANGELO M. SALA: There is no denying the difficulties of a histologic classification of these thymic tumors, and yet I feel that a classification ought to be attempted because it is possible in practically all cases. The term thymoma should be dropped as both evasive and meaningless.

The leukemic conversion spoken of by Dr. Foot occurs only in the lymphosarcoma group. Symmers described three such cases in his report; I have observed one. There is a question in these cases whether one is not dealing from the beginning with a leukemia, of which the thymic enlargement is a manifestation.

Dr. Foot is right when he says that distant metastases from these tumors are not as common as this small series would lead one to believe. It is a chance occurrence that of our three cases in which autopsy was performed, two showed distant metastases.

CYSTIC DEGENERATION OF THE POSTERIOR LOBE OF THE PITUITARY GLAND. DOMINIC A. DE SANTO (by invitation).

Cystic degeneration of the posterior lobe of the pituitary gland was encountered in a Russian Jew, 32 years old, who weighed approximately 450 pounds (200 Kg.) and gave a history of increasing obesity since the age of 20, voracious appetite, pathologic somnolence resembling true narcolepsy, severe frontal headache and polyuria. Clinically, the patient showed exophthalmos, hypertension, genital atrophy, generalized obesity, accentuated over the abdomen and thighs, a narcolepsy-like syndrome consisting in prompt onset of sleep almost immediately after sitting down, a diminished, instead of an increased, tolerance for carbohydrate, and a basal metabolic rate within normal limits.

At autopsy, death appeared to have been caused by hypertensive heart disease in congestive failure. The diencephalic area showed no gross alterations and unfortunately was not preserved for study. The sella turcica appeared normal; the pituitary gland was of normal size, but the posterior lobe appeared bulbous and on sagittal section showed a gross cystlike alteration. The cyst contained shreds of granular debris.

On serial section, approximately three fourths of the posterior hypophysis appeared destroyed. An irregular cavity was found without a lining and without significant alterations in the small surrounding rim of tissue. Diagnoses of gumma, tubercle, necrotic tumor, embolus, ischemic softening and retention cyst of the pars intermedia were considered and excluded. An area in the anterior lobe showed a localized overgrowth of fibrous tissue with focal disintegration of a few acini. The anterior lobe was otherwise normal.

The thyroid gland showed slight colloid transformation. The testes showed striking changes consisting of a diminution in the size and number of the tubules and in the number of interstitial cells.

Whatever the cause of the lesion, it was considered to be chronic, and to it was assigned responsibility for the symptoms.

It is recognized, however, that in the absence of diencephalic studies, the whole picture could be equally well ascribed to some unnoticed lesion of the tuberal region, especially since the patient had suffered previously from attacks of grip. From this point of view the syndrome would probably be postencephalitic.

DISCUSSION

ALFRED PLAUT: Dr. De Santo mentioned our work published eleven years ago. This study was begun by Simmonds, the man for whom hypophyseal cachexia is named. I repeated his work in thirty-five autopsies on patients with pyemia, and metastatic lesions were found in the hypophysis in seventeen cases. All these, however, were cases of true pyemia. I should not venture to say that from this high percentage one could draw any conclusion as to a possible relation between disturbances of internal secretion and preceding ordinary infections of the throat. Tonsillitis and true staphylococcic pyemia are widely differing diseases. It seems rather difficult to me to obtain a reliable statistical basis for establishing a connection between the frequent infections of the throat and the occurrence of disturbances in internal secretion.

The case reported by Dr. De Santo is unusual, and it is difficult to say anything about it. It would be necessary to know more details about the lesion in the posterior lobe, for instance, whether there was necrosis, neuroglial overgrowth or epithelial structures pointing to a cyst. Why are the changes which the patient exhibited ascribed to a disturbance in the posterior lobe of the hypophysis? The patient's symptoms certainly were not those which one is accustomed to see in disease of the posterior lobe. Were there any changes in the blood vessels supplying the hypophysis? Since the original title of the paper mentioned ischemic change, I have brought lantern slides illustrating two instances of true ischemic changes in the hypophysis. Such lesions are rare and are often overlooked because the hypophysis is not examined.

The first case was that of a boy 11 years old who died soon after the onset of the basal streptococcic meningitis which had its origin in the sphenoid sinus. Even with the naked eye one could see the extensive central necrosis in the anterior lobe of the hypophysis. There was no inflammation in the peripheral layers of the anterior lobe. Obviously the thick, purulent exudate had blocked the tissue spaces and the lumens of the vessels in the surroundings of the hypophysis, thus leading to a true ischemic necrosis.

The second instance of necrosis in the anterior lobe was in a man 82 years old. The slide shows the very narrow lumen of one hypophyseal artery. One is not astonished, therefore, to see the necrosis in the anterior lobe.

If at autopsy the hypophysis received the attention that one is accustomed to give to the suprarenal glands or to the spleen, such lesions probably would be found more frequently.

SOLOMON SILVER: My attention was primarily attracted by the idea of ischemic degeneration of the posterior lobe of the pituitary gland, but apparently Dr. De Santo did not present the case as one of this condition. I find this particularly interesting because, so far as I know, ischemic degeneration occurs

only in the anterior lobe. Apparently, as was pointed out twenty years ago by Simmonds, the arteries of the anterior lobe are functionally end-arteries, whereas the arteries in the posterior lobe anastomose with each other, and although embolism of the posterior lobe may be more common, subsequent changes, especially with regard to infarction, are rare; in most of the cases I was able to collect in a rather extensive survey of the literature, the pathologic changes in the posterior lobe were scanty compared to those in the anterior lobe.

Considering Dr. De Santo's case clinically, it is unfortunate that the diencephalic areas were not investigated. It is hard to believe, in view of all the recent work on the nature and the cause of polyuria and polydipsia, that the posterior lobe is involved. One must accept the fact that the posterior lobe can be completely removed without giving any of these symptoms, and that in the absence of the posterior lobe, properly placed diencephalic punctures can give rise to all of the symptoms. It seems to me that the clinical picture was diencephalic. This cannot be proved in the absence of the tissue, but changes in the posterior lobe even more extensive than those shown seldom give rise to this picture unless the tumor has spread to the diencephalic areas. I should tend to believe that the whole syndrome was diencephalic, probably on the basis of a "missed" encephalitis.

ALFRED PLAUT: Ischemic lesions are much more frequent in the anterior lobe, but they occur in the posterior lobe also.

DOMINIC DE SANTO: In regard to the title of this presentation, in studying serial sections I encountered certain changes in the vessels and slight thickening of the intima and of the elastic tissue which on reconsideration I thought were the normal concomitant of the hypertension. It occurred to me then that this condition might have been ischemic atrophy; but I said at the outset that I withdrew that suggestion, because it would be difficult to maintain the premise that there was ischemic degeneration. I do not know the nature of the condition.

As to the histologic appearance of the surrounding rim of tissue, there was no evidence, so far as I could see, of glial overgrowth, nor was there any deviation from the normal appearance of the pituitary gland that shed any light as to what the condition was. There was no endothelial lining. In serial sections the cyst did not communicate with the colloid cysts of the pars intermedia, so that it undoubtedly was not a retention cyst of the pars intermedia, such as might conceivably develop.

As to whether the symptoms were due to this lesion, that is difficult to state. I considered the possibility of the condition being postencephalitic, particularly since the patient had had several attacks of what apparently was grip. On the other hand, nothing like this has been reported in encephalitis, and one cannot ignore the lesion.

As to whether all of these symptoms were due exclusively to tuberal lesions, I do not know that that has been definitely proved. It seems to be the belief of Cushing and others that the pituitary gland and the hypothalamus form a system, and that a modified so-called hypopituitary syndrome may result from lesions anywhere in this pituitary-mesencephalic system. I do not agree that it is entirely established that the posterior lobe of the pituitary gland cannot give rise to deficiency symptoms of the type described, even though tuberal extirpation may result experimentally in hypogenitalism, obesity and high carbohydrate tolerance, polyuria and other conditions, and even though the original hypophysectomies have been criticized, because it has been maintained that in removing the pituitary gland the tuber has been accidentally injured. In further experiments Cushing showed that these so-called tuberal symptoms have developed when merely the hypophyses was destroyed. In other words, if all the symptoms are due to the tuber cinereum, the pituitary gland has practically no function. I think that the lesion must have some bearing on the development of the symptoms, but I have no way of proving it.

MYOBLASTOMA OF STRIATED MUSCLE. PAUL KLEMPERER.

Neoplasms composed of myoblasts, the ancestral cells of striated muscle, were first described by Abrikossoff in 1926. There is now a total of about fifty recorded observations, if one includes those which are casually mentioned in discussions occasioned by the report of such cases. This indicates that this variety of tumor is certainly not uncommon. Because there are only two reported cases in the American and English literature, and these were recorded under the term of "rhabdomyoma of the tongue" (Keynes, Dewey), a report is here made of six additional observations collected in the last four years. The histologic appearance of these tumors is uniform. They are composed of large round or polyhedral cells and ribbon-like syncytial masses which are surrounded by slender collagen fibers. The most characteristic feature, however, is the pronounced granular structure of the cytoplasm.

In the differential diagnosis the xanthomas must be chiefly considered, a fact which has been stressed by several writers. In fact, this mistake in diagnosis has occasionally occurred (Peyron). However, the absence of fat in frozen sections rules out xanthoma, although the cells in paraffin sections resemble those of xanthoma.

The tumors that I have observed were localized in the skin (three cases), the tongue, the vocal cords and the gastrocnemius muscle, respectively. A survey of all the cases reported shows the following distribution: tongue, twenty-one cases; maxilla (congenital epulis), four; skin, four; vocal cords, three; mandible, two; breast, two; lip, one, and upper part of the esophagus, one.

This summary reveals a conspicuous preference for the upper digestive and respiratory tract, with the tongue as the most frequent site of localization.

As to malignancy, there was no recurrence in any of the cases here reported from six months to three years after excision. Only one case in the literature (Meyenburg) was malignant as evidenced by repeated recurrence with local invasion after operation.

The myoblastomas of striated muscle represent a well defined oncologic group of practical importance.

DISCUSSION

NATHAN CHANDLER FOOT: Just this afternoon I was puzzling over a tumor which was identical with those which Dr. Klemperer has shown. It was taken from a Negress, 74 years of age. It had been present for a number of years and had been treated in various ways. It was finally removed by a surgeon with the tentative diagnosis of carcinoma. It showed little epithelial proliferation, as Dr. Klemperer mentioned, but showed the peculiar infiltrating growth of these granular cells. I was thinking of making a diagnosis of xanthoma, although I was waiting until tomorrow for another look at the tumor. Dr. Klemperer has made the diagnosis easy.

Book Reviews

Arteriosclerosis: A Survey of the Problem. A publication of the Josiah Macy, Jr., Foundation. Edited by Edmund V. Cowdry, Washington University, St. Louis. Price, \$5. Pp. 617, with 88 figures. New York: The Macmillan Company, 1933.

This book presents the results of an earnest cooperative attempt to promote the investigation of arteriosclerosis by a survey that would indicate promising lines of approach. It contains twenty-one articles on various aspects of arteriosclerosis by well qualified writers, many of whom are widely known from their previous work in this field. In the foreword and preface Ludwig Kast, the director of the Josiah Macy, Jr., foundation, and Edmund V. Cowdry, the editor, explain fully the considerations that have guided them in the preparation of the book. Dr. Kast expresses the hope that the survey will be accepted by investigators, clinical as well as experimental, as an invitation for suggestions "as to how to move closer through joined efforts to an understanding of 'arteriopathy.'" And Dr. Cowdry trusts that the book will be helpful to investigators, physicians and students of medicine. In the introduction Ludwig Aschoff discusses the essential nature of arteriosclerosis with a view to defining the process as clearly and as closely as possible. "To sum up, we understand by arteriosclerosis a chronic disturbance of the vessels which manifests itself by deposits of the most varied kinds in the vascular walls and which becomes irreversible on reaching its climax in vessels impaired by changes attending the process of aging with resulting deformation of the lumen and brittleness of the vascular walls." Aschoff regards changes in the ground substance as of great importance in the development of arteriosclerosis. Esmond Long writes an interesting and lucid historical review of the development of knowledge of arteriosclerosis, with emphasis on the recent views of its etiology. Then follow chapters on the structure and physiology of blood vessels (E. V. Cowdry), the physical properties of arteries in health and in disease (Crichton Bramwell) and the mineral constituents of blood vessels as determined by incineration (A. Policard). Policard writes: "The importance of the techniques outlined in this chapter is that they permit the investigator to determine accurately the very earliest changes in mineral constituents in beginning arteriosclerosis. It is these earliest lesions which, when examined from every angle, may be expected to afford clues to the etiology of the condition. As I have already stated, work along this line has a definite bearing upon physical changes in the elastic fibers and upon the interesting theory of Wells on the aging of colloids. It should be followed." The statistical aspect of arteriosclerosis is discussed by Edgar Sydenstricker; the relation of arteriosclerosis in lower mammals and birds to the human disease is presented by Herbert Fox (good figures); the rôle of climate and race is the topic of the chapter by Percy Stocks, and nutrition in relation to arteriosclerosis is considered by Soma Weiss and George R. Minot. William Ophüls, who died recently, writes on the pathogenesis. N. Anitschkow concludes his chapter on experimental arteriosclerosis (illustrated) as follows: "Feeding with cholesterol is the only method which makes it possible for us to produce in certain species of animals changes that may be regarded as equivalent to those typical of human atherosclerosis. The experimental investigations based on this method, which will be supplemented by further experiments, have opened the way to a systematic analysis of the pathogenesis and etiology of the disease. Undoubtedly the results thus obtained will also provide valuable indications in respect to prophylactic and therapeutic measures." In his important discussion of the chemistry of arteriosclerosis, H. Gideon Wells supports the view that it "depends primarily on changes in the elastic tissue that reduce its resiliency and lead to arterial dilatation"; the change in the elastic fibers in arteries "is only that always produced sooner or later

as the natural fate of all elastic colloidal gels"; intimal thickening, lipoid deposits and calcareous deposits are secondary processes. After reviewing the rôle of infections, William G. MacCallum finds "but little evidence in favor of the idea that infections, whether acute and chronic, play a great part in the pathogenesis of arteriosclerosis." Then come instructive chapters on regional arteriosclerosis: retina (J. S. Friedenwald), brain and cord (Stanley Cobb and Daniel Blain), coronary (good illustrations) and pulmonary arteries (Howard T. Karsner, two chapters) and abdominal viscera and extremities (E. T. Bell). The relation of hypertension to arteriosclerosis is analyzed by Fritz Lange, who holds that hypertension is a symptom the cause of which remains to be found. (In this chapter the German term "hypertonía" is used in place of hypertension, without any apparent justifiable reason.) George Dee Williams contributes a chapter on the hereditary aspects of arterial hypertension. John Wyckoff concludes his chapter on the treatment of arteriosclerosis with the statement that "to institute rational treatment much more searching investigation is required." At the end of each of these chapters is a list of select references. In the final chapter Alfred E. Cohn writes a constructive and judicious summary of the views and suggestions of his fellow contributors. This summary merits close and careful study. There are good subject and author indexes. A lighter and duller paper might have been used. The book weighs nearly 4 pounds. The articles reflect the individual views of the authors. To discuss in detail these views, often simply and directly expressed, is out of the question. No formal agreements are recorded either as to pressing problems or as to investigative approach. But there is the significant, even if tacit, acceptance of the powerful integrative principle that arteriosclerosis, no matter how defined, is the result of factors involving the organism as a whole. The hopes of the sponsors of the book that it may advance the understanding of arteriosclerosis are justified.

Urine and Urinalysis. By Louis Gershenfeld, Ph.M., B.Sc., Ph.D., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science. Price, \$2.75, net. Pp. 272, with 36 engravings. Philadelphia: Lea & Febiger, 1933.

The first part of this book deals briefly and in elementary fashion with the structure and function of the kidneys; with urine, its physical characteristics and chemical composition, and with the abnormal constituents of urine. The second part deals with urinalysis, with chapters on qualitative tests, quantitative estimations and microscopic examination of urine. In the third part special urinary tests are described. There is an appendix on special apparatus and on reagents. The introduction contains a condensed review of the history of urinalysis. The illustrations represent for the most part apparatus, some of which, e. g., the hand centrifuge (fig. 15), seems rather antiquated. The presentation is concise and orderly. The various methods of analysis are described clearly. The book may be recommended as a reliable guide in the technic of urinalysis. No attempt is made to interpret results. Its sole object is to guide the analyst to secure accurate data for clinical use.

A Text-Book of Neuropathology. By Arthur Weil, M.D., Associate Professor of Neuropathology, Northwestern University Medical School, Chicago. Cloth. Price, \$5. Pp. 335, with 260 engravings. Philadelphia: Lea & Febiger, 1933.

The object of this book is "to give a review of the present stage of our knowledge of neuropathology," which "is the study of the nervous tissue in disease and the determination of deviations of its structure from the normal." The book deals principally with the microscopic study of these changes. The chapter headings give a good idea of its scope: changes produced by autolysis and fixation, diseases of the ganglion cells, the glia and its pathology, pathology of the myelin sheaths and the axis cylinder, anemic softening, arteriosclerosis,

inflammation, infections, intoxications, injuries, degenerative diseases, tumors, congenital malformations, appendix. In the appendix are tables of the weight of the brain, directions for the postmortem examination and fixation of the central nervous system and descriptions of staining methods. At the end is a list of references to important recent work in neuropathology arranged according to the order of the chapters in the text. For ready reference this does not seem to be a good arrangement. In general, the descriptions of the microscopic appearances of the nerve tissues in disease are accurate and clear. The illustrations, mostly original, are excellent. The book will be of much help to students of neuropathologic histology. In fact, it is so predominatingly histologic in scope that it hardly deserves the title of "A Text-Book of Neuropathology." To merit this title fully extensive expansion is required. This may be possible in a new edition. If the call comes for a new and revised issue, certain matters and questions should receive special attention. Does the frequent use of German words help the presentation? The following German words are now used: Wasserfehler, aequivalent Bild, homogenisierende Zellenerkrankung, Stäbchenzellen, Glia-rasen, gemästete, Wetterwinkel, fohstich Encephalitis, Lückenfelder, Anfälligkeit and Aufbrauch. Certainly the meaning of most of these words can be conveyed adequately by simple English terms. In an eventual expansion of the book thorough attention should be given to the systematic description of gross appearances. At present, for instance, nothing is said about the gross characteristics of the brain in acute poisoning with carbon monoxide and of different tumors of the brain. The highly important subject of meningeal hemorrhage merits systematic treatment in a neuropathologic discussion. The section on *Blastomyces* infection (p. 172) needs revision in any case. What is *Sporotrichon*? Should not "functional psychoses," epilepsy and senile dementia be mentioned? Is not herpes zoster, which is not mentioned, a disease of the nerve tissue? Should not the cerebrospinal fluid be discussed in detail? Is the use of the word toxin as synonymous with poisons or morbidic substances of any kind or nature justifiable? Are not the phrases commonly used about toxins in this general sense and their effects on cellular structure just cloaks of ignorance of misleading verisimilitude? What is known about the toxins of the spirochete of syphilis? If it is decided to limit further editions of the book to neuropathologic histology, the field it now covers satisfactorily, such limitation should be indicated by a change in the title.

The History and Epidemiology of Syphilis. The Gehrman Lectures, University of Illinois, 1933. By William Allen Pusey, A.M., M.D., LL.D., Emeritus, Professor of Dermatology, University of Illinois, Sometime President of the American Dermatological Association and of the American Medical Association. Price, \$2. Pp. 105. Springfield, Ill.: Charles C. Thomas, 1933.

These three lectures are an elaboration of parts of the author's monograph on "Syphilis as a Modern Problem," published in 1915. The history, epidemiology and control of syphilis are reviewed in the light of the knowledge and experience of today. The first lecture describes graphically the startling appearance in southern Europe at the end of the fifteenth century of a new disease, somewhat later called syphilis, which spread rapidly in all directions. The record is unique—there is no record of any other great disease that has established itself with such precision and rapidity. In view of the lack of any indications of the presence of syphilis earlier in Europe (and Egypt) and in view of the evidence unearthed by Montejo y Robledo that syphilis was brought to Spain by the sailors of Columbus, as well as other considerations, the author concludes that "the preponderance of evidence for the American origin of syphilis is overwhelming." In the second lecture the growth of the knowledge of syphilis from the earliest descriptions of its manifestations in 1496 down to today is detailed clearly and instructively. This growth coincides with the growth of medicine in general.

The disastrous effect of John Hunter's experiment on himself and the gradual groping back into the right road are admirably sketched. Copies of old illustrations, some of them among the earliest dealing with syphilis, and many portraits of the great students and investigators of syphilis add to the interest of these two lectures. The third lecture is devoted to a discussion of the spread or epidemiology of syphilis under four headings: the reservoir of infection, the infecting organism, the susceptible host and the means of transmission. The conclusion is that syphilis can be controlled if handled as a sanitary problem. "We should strive to make it as far as possible such a problem." The book should be read widely by persons who have a special interest in syphilis. It has educational value in a large sense because it tells so well how syphilis has come to be understood as fully as it is and how thoroughly the ground for its control has been prepared.

Surgical Pathology. By William Boyd, M.D., M.R.C.P., F.R.C.P., Professor of Pathology, University of Manitoba. Third edition. Cloth. Price, \$10. Pp. 866, with 490 illustrations. Philadelphia: W. B. Saunders Company, 1933.

The first edition of this book was published in 1925 and was well received. The second edition was published in 1929. The appearance of the third edition indicates its continued usefulness and popularity. Considerable appropriate new material has been introduced, and many of the sections have been revised or rewritten, but the size of the volume has not been increased. The book has been brought well up to date and may be recommended as a well written and useful handbook in its field.

Books Received

THE GREAT DOCTORS: A BIOGRAPHICAL HISTORY OF MEDICINE. Dr. Henry E. Sigerist, Professor of the History of Medicine, Johns Hopkins University. Translated by Eden and Cedar Paul. Price, \$4. Pp. 436, with over 60 illustrations. New York: W. W. Norton & Company, Inc., 1933.

BACTERIAL INFECTION, WITH SPECIAL REFERENCE TO DENTAL PRACTICE. J. L. T. Appleton, Jr., B.S., D.D.S., Professor of Microbiology and Bacteriopathology, the Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania. Second edition. Price, \$7, cloth. Pp. 654, with 122 engravings and 4 colored plates. Philadelphia: Lea & Febiger, 1933.

FOOD, NUTRITION AND HEALTH. E. V. McCollum, Ph.D., ScD., and J. Ernestine Becker, M.A., Professor and Associate of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University. Third edition. Price, \$1.50, postpaid. Pp. 146. Baltimore: E. V. McCollum and J. Ernestine Becker, 1933.

COLOUR VISION REQUIREMENTS IN THE ROYAL NAVY: XII. REPORTS OF THE COMMITTEE UPON THE PHYSIOLOGY OF VISION. Medical Research Council, Special Report Series, No. 185. Price, 1s. Pp. 58. London: His Majesty's Stationery Office, 1933.

LES TROUBLES DE L'ÉLIMINATION URINAIRE DE L'EAU: ÉTUDE PHYSIO-PATHOLOGIQUE ET CLINIQUE. Jules Cottet, Ancien interne des hôpitaux de Paris. Price, 32 francs. Pp. 212. Paris: Masson et Cie, 1933.

ATYPICAL FORM OF PAGET'S DISEASE APPEARING AS GENERALIZED OSTEOSCLEROSIS

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In the domain of bone disease, unlimited information is yet to be gleaned by continued painstaking pathologic investigation. Intensive study would undoubtedly be of prodigious value in the clarification and interpretation of many puzzling features of Paget's disease. Only recent work has revealed that the hitherto accepted concept of this disease is neither complete nor comprehensive. The prevailing premises that the condition is rare, that the tibia is the bone most frequently involved and that the calvarium is generally thickened no longer hold in the light of these studies. Neither does the view wholly obtain that the changes in the bones are necessarily associated with softening, thickening and deformity, producing a clinical picture such as was originally drawn by Paget.¹ Through Schmorl's observations it became evident that the vertebrae (particularly the lumbar) and the sacrum are most susceptible to involvement by this disease. Frequently, the lesion is limited to only one or more of the lumbar vertebrae or merely to a portion of the sacrum. In such instances, there need be no clinical manifestation of the condition, and roentgenographically the implication may not even be discernible. Furthermore, by systematic post-mortem examination of bones, he found that about 3 per cent of those in persons past 40 years of age were affected by some degree of Paget involvement.²

In a review³ written a short while ago, a rather extensive survey was made of Paget's disease. Special emphasis was laid on the histologic criteria for diagnosis (the mosaic architecture), the evolutionary progress of the changes in both cortical and spongy bone and the activity of the periosteum in initiating thickening of tubular bones (as demonstrated by a case independently observed). Freund⁴ was the first who was able to demonstrate conclusively that periosteal proliferation sometimes reaches such proportions as to be easily discernible with the naked eye. In my case it was evident that gross subperiosteal new

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1. Paget, J.: *Tr. Roy. M. & Chir. Soc., London* **60**:37, 1877.
2. Schmorl, G.: *Virchows Arch. f. path. Anat.* **283**:694, 1932.
3. Jaffe, H. L.: *Arch. Path.* **15**:83, 1933.
4. Freund, E.: *Virchows Arch. f. path. Anat.* **274**:1, 1929.

bone formation was only an exaggeration of the process that ordinarily leads to thickening of the bone in Paget's disease and that generally can be seen only under the microscope.

The horizon embracing Paget's disease is constantly widening. Pines⁵ (working under Erdheim) has even more recently described a porotic calvarium which was not thickened and which, in the gross, suggested Recklinghausen's disease rather than Paget's disease. Microscopically, in addition to its porotic areas, certain sclerosed regions presented primitive bone centrally and lamellar bone peripherally, with the Paget mosaic architecture in the lamellar bone. This case, which was considered an unusual porotic form of Paget's disease (confined to the cranial bones), seems to throw some light on those poorly understood lesions of the calvarium which are so difficult of interpretation and which have heretofore been described, especially roentgenographically and clinically, under divers titles. Pines' pathologic study may be of great value in clarifying the understanding of the calvarial lesions described as circumscribed osteodystrophy.⁶ Furthermore, it is definitely helpful in interpreting the significance of the circumscribed porotic lesions which occasionally appear in the calvarial bones (with or without Paget-like involvement in other portions of the calvarium or of other bones).⁷

The study of a case which further supports the possibilities of variation in the pathologic manifestations of Paget's disease is here recorded. The calvarium, spine, innominate bones, sternum and ribs removed from a patient who died of uremia showed an advanced osteosclerosis which was intense in certain areas. The calvarium was heavy and sclerotic, but was not noticeably thickened. Paget's disease was nowhere plainly suggested in the gross, except possibly in the ilia. Microscopically, the osteosclerosis, except in the more intense areas, was not associated with scarring of the marrow (the marrow remained myeloid and fatty); the trabecular thickening was everywhere the result of slow new bone deposition following slowly progressing resorption. Such thickened trabeculae were constituted of lamellar bone and showed an increased number of cement lines. The cement lines, on the whole thin and somewhat irregular, separated numerous fragments of lamellar bone. The Paget nature of the osteosclerosis was strongly suggested by this histologic appearance. It was confirmed to a greater degree by the microscopic features in the areas of more intense sclerosis where complete trabecular reconstruction had occurred, where the picture in

5. Pines, B.: *Virchows Arch. f. path. Anat.* **287**:714, 1933.

6. Frangenheim, P.: *Verhandl. d. deutsch. path. Gesellsch.* **21**:49, 1926.

7. Sosman, M. C.: *Radiology* **9**:396, 1927. Schueller, A.: *Med. Klin.* **25**: 631, 1929. Weiss, K.: *Fortschr. a. d. Geb. d. Röntgenstrahlen* **41**:8, 1930; **42**: 376, 1930. Meyer-Borstel, H.: *ibid.* **42**:589, 1930. Kasabach, H. H., and Dyke, C. G.: *Am. J. Roentgenol.* **28**:192, 1932.

regard to the mosaic reached a somewhat more characteristic appearance and where the myeloid and fatty marrow had been converted into fiber marrow. But even in such areas, the gross appearance was not that of typical Paget's disease. Thus, in this case, the gross pathologic changes of Paget's disease were manifested essentially by an osteosclerosis. There can be no doubt that in the diagnosis of Paget's disease, histologic appearances take precedence over clinical features and even over gross aspects.

Several references have until now been made to the mosaic architecture of typical Paget bone. The newly formed lamellar bone in Paget's disease has this distinctive appearance, and to Schmorl must be credited the bringing into relief of the value of this rather specialized histologic feature for diagnosis. Completely and typically developed new Paget bone is found, on microscopic examination, to consist of irregular segments of lamellar bone (*breccie*), which are separated by short, irregular and often somewhat toothed cement lines. Furthermore, in Paget lamellar bone that is being rapidly built up, the cement lines may be short and stain deeply. Thus, an area of bone totally transformed and completely involved by typical Paget's disease consists, microscopically, of tiny fragments of lamellar bone fitted into one another like an irregular mosaic, with little tendency for the bone fragments (as pointed out by Freund) to be arranged about vessel canals to form haversian systems. The more rapid and florid the progress of Paget's disease, the more characteristically does the mosaic appearance develop; healing of Paget's disease is associated with a tendency for the mosaic arrangement to disappear. The slow progress of the development of the osteosclerosis in the case here reported was the factor to some degree modifying the typical mosaic arrangement.

REPORT OF A CASE

The patient, aged 58, a house painter, gave a history of one lead colic attack at the age of 38 and typhoid fever at 28; he had had swelling of the ankles and dyspnea on exertion, with an attack of cardiac pain four years before; he entered the hospital specifically for inability to void urine without catheterization. Examination disclosed prostatic enlargement, cardiac hypertrophy and chronic nephritis. There was 2 plus albumin in the urine, with fixation of the specific gravity at about 1.010; on admission blood analysis showed 60 per cent hemoglobin, 3,840,000 red cells and 11,300 white cells (the differential count showed nothing unusual); there was no basophilic stippling; the blood urea was 42 mg. per hundred cubic centimeters, and it rose to 80 mg. before death; the blood pressure was 134 systolic and 90 diastolic.

Two days after a transurethral resection of the prostate under spinal anesthesia, the patient became seriously ill, with elevation of temperature and evidences of meningeal irritation. Lumbar puncture showed a turbid spinal fluid with a cell count of about 2,000, normal sugar and sterile culture; the spinal cell count finally diminished to about 100 cells. He was treated by spinal drainage, and on culture

several of numerous specimens showed pleomorphic, hemolytic streptococci, which grew slowly. Though the meningeal irritation receded, evidences of increasing uremia appeared, and finally pulmonary edema developed and the patient died.

Pathologic Changes.—Other than the changes referable to the bones, the gross and microscopic examinations disclosed contracted kidneys on an arteriovascular basis, arteriosclerosis of the aorta and coronary arteries, terminal acute pericarditis, cardiac hypertrophy and dilatation, bilateral hydrothorax, beginning bronchopneumonia and low grade meningitis (there was a scattering of leukocytes over the pia-arachnoid with very little fibrin).

Vertebral Column: Gross appearance. The vertebral column was removed from the fourth dorsal vertebra down through and including the sacrum and coccyx.

A slight degree of upper dorsal kyphosis existed, and there was some diminution in flexibility of the upper dorsal spine. The individual vertebrae appeared to be of good size. While normal values for measurement are not readily obtainable and comparisons are unsatisfactory because of considerable individual variations, nevertheless, the lumbar vertebrae gave the impression that they were slightly larger than normal in the anteroposterior diameters. The upper and lower surfaces of the dorsal vertebrae were on the whole quite straight; these surfaces of the lumbar vertebrae were slightly depressed in conformity with the slight expansions of their disks.

On sagittal section, the disks between the lumbar vertebrae were found slightly expanded, while the others were of about average thickness. Throughout, the intervertebral disks were brown (fatty degeneration being clearly discernible in the gross); the brown degeneration of the lumbar intervertebral disks was most prominent. The turgor of the nuclei of the disks was for the most part well maintained; there were small prolapses of the intervertebral disks from the upper surface of the tenth, eleventh and twelfth dorsal disks (fig. 1). A small prolapse from the lower surface of the second lumbar disk was apparent. There was considerable tendency to calcification of the anterior portions of the annuli fibrosi of the dorsal disks. The disk between the fifth lumbar and the sacral promontory was partially calcified; the first sacral disk (as well as the lower two) was still present although calcified; the second and third sacral disks had almost completely vanished; the coccygeal disks were present. Lipping of the upper and lower margins of the vertebral bodies was clearly observed in the macerated portion of the spine; this was the result of osteophytic overgrowth below the anterior ligaments. Laterally, between the seventh and eighth dorsal vertebrae, two large apposed and overlapping osteophytes were seen.

The appearance of the spongiosa of the vertebrae and sacrum was the noteworthy feature in the sagittal section of the spine. The trabeculae everywhere were thickened, and the spongy structure was quite compact (fig. 1). The thickening of the trabeculae had resulted in a reduction in size and a change in the direction of the marrow spaces; this applied to the bodies and processes alike. (The spongiosa of a normal vertebral body is delineated by major vertical lines and minor horizontal lines forming a honeycombed structure with fairly regular marrow spaces.) In these vertebral bodies the direction of the trabecular lines was completely distorted; the marrow spaces were marked by irregularity of shape and size, and were greatly reduced (many were so small as to be discernible only in the macerated specimen).

Moreover, certain vertebrae had dense sclerotic patches which were strikingly prominent in the wet preparation. One such area was located in the posterior half of the body of the first lumbar vertebra extending from disk to disk (fig. 1). In



Fig. 1.—A wet specimen from the spine, including the tenth, eleventh and twelfth dorsal and the first lumbar vertebrae and their intervertebral disks. The tenth, eleventh and twelfth dorsal disks show small prolapses through their upper surfaces. The spongy trabeculae of the vertebral bodies are evidently thickened, and the marrow spaces present marked irregularity in size and shape. A patch of dense sclerosis is observed in the posterior half of the first lumbar vertebra and in the spinous process of this vertebra; the dense sclerosis in the body and spinous process of the eleventh dorsal vertebra is also clearly evident.

the wet preparation, these intensely sclerotic regions were characterized by a whitish-yellow coloration, a smooth cut surface and a dense consistency when scraped with the nail. Under a hand magnifying glass, such an area in a macerated preparation displayed the features of the adjoining less sclerosed spongia to a markedly intensified degree by virtue of its greater compactness



Fig. 2.—Macerated preparation from the other half; it includes the tenth, eleventh and twelfth dorsal and the first and second lumbar vertebrae. All of the vertebrae show osteosclerosis with the more intensified sclerosis in the eleventh dorsal and the first lumbar vertebrae.

(fig. 2). The spinous process of this body similarly showed dense sclerosis. An area of equally intensified sclerosis was observed in the posterior portion of the body of the eleventh dorsal vertebra, while the entire body of the fourth dorsal vertebra was so converted.

Thus, the vertebrae manifested generalized osteosclerosis of the bodies and processes, which was intensified in certain of the bodies, particularly in the first lumbar, the eleventh dorsal and the fourth dorsal; in these vertebrae, the intense sclerosis extended into the processes.

On sagittal section of the sacrum, sclerosis was again apparent, being quite intense in its upper two-thirds, most of which was very compact. This process was more or less uniform, extending from the anterior to the posterior surfaces.

Microscopic appearance. Sections for histologic study were taken from a number of different vertebral bodies and from the sacrum and coccyx. In regard to the major pathologic changes, the descriptions will be confined (1) to the appearance of the tenth dorsal vertebra, which showed the generalized but less intense osteosclerosis, (2) to the first lumbar vertebra, which in addition had a large patch of more intense sclerosis posteriorly, and (3) to the upper portion of the sacrum, which evidenced a more or less generally intense sclerosis.

1. The tenth dorsal vertebra presented a general trabecular thickening even under the lowest magnifications (fig. 3*A*). In such a survey it could be seen that the thickened trabeculae were composed throughout of lamellar bone, while the narrowed intertrabecular marrow spaces contained myeloid and fatty marrow which was not apparently abnormal. Immediately beneath the intervertebral disks, the spongiosa was, on the whole, most compact. Two small intervertebral disk extensions, one from the upper and the other from the lower disk, were observed, but the protrusions were limited to small zones immediately beneath the defective annuli. There was no framing or compacting of the sclerotic trabeculae at the anterior or posterior margins of this body.

Higher magnification disclosed microscopic abnormality of all the thickened trabeculae (fig. 3*B*). This deviation from the normal was evidently the result of gradual resorption occurring on the surfaces of many of the trabeculae, followed by new bone deposition. Many of the trabeculae, showing resorption on the surfaces, contained osteoclasts in sparse numbers in Howship's lacunae; where resorp-

8. Comparison of the sagittal section of this spine with that of a spine involved by typical Paget's disease would show striking contrasts. In the latter type of involvement, it is to be observed that the vertebral bodies show thickened, closely set trabeculae framing the body peripherally. Furthermore (in contradistinction to the appearances observed in the vertebral bodies of the case reported), the more centrally placed trabeculae are much fewer in the more typical involvement. They usually are distinct as pillars with irregular surfaces. The differences in appearance between the typically involved spine and the spine under observation are also clearly marked on roentgenographic examination. In the usual type of involvement, the roentgenogram of a spine extirpated from the body will show the peripheral condensation of trabeculae and the central rarefaction, which, of course, this spine did not evidence. It did show a diffuse sclerosis, and it is worthy of mention that an antemortem roentgenogram did not suggest the presence of Paget's disease, although it could be recognized in the plates that a sclerosis existed. It is especially noteworthy that in this spine, although the involvement was diffuse, no serious deformations in the shape of the vertebral bodies had occurred. This often takes place in the bodies of spines with the more typical Paget's disease; in such the more common deformity is a reduction in the superior-inferior diameter of the body and an increase in the anteroposterior diameter (the latter being due to periosteal growth). While there was no reduction of the superior-inferior diameter in this case, the lumbar vertebrae presented a possibly slight increase in their anteroposterior diameters.

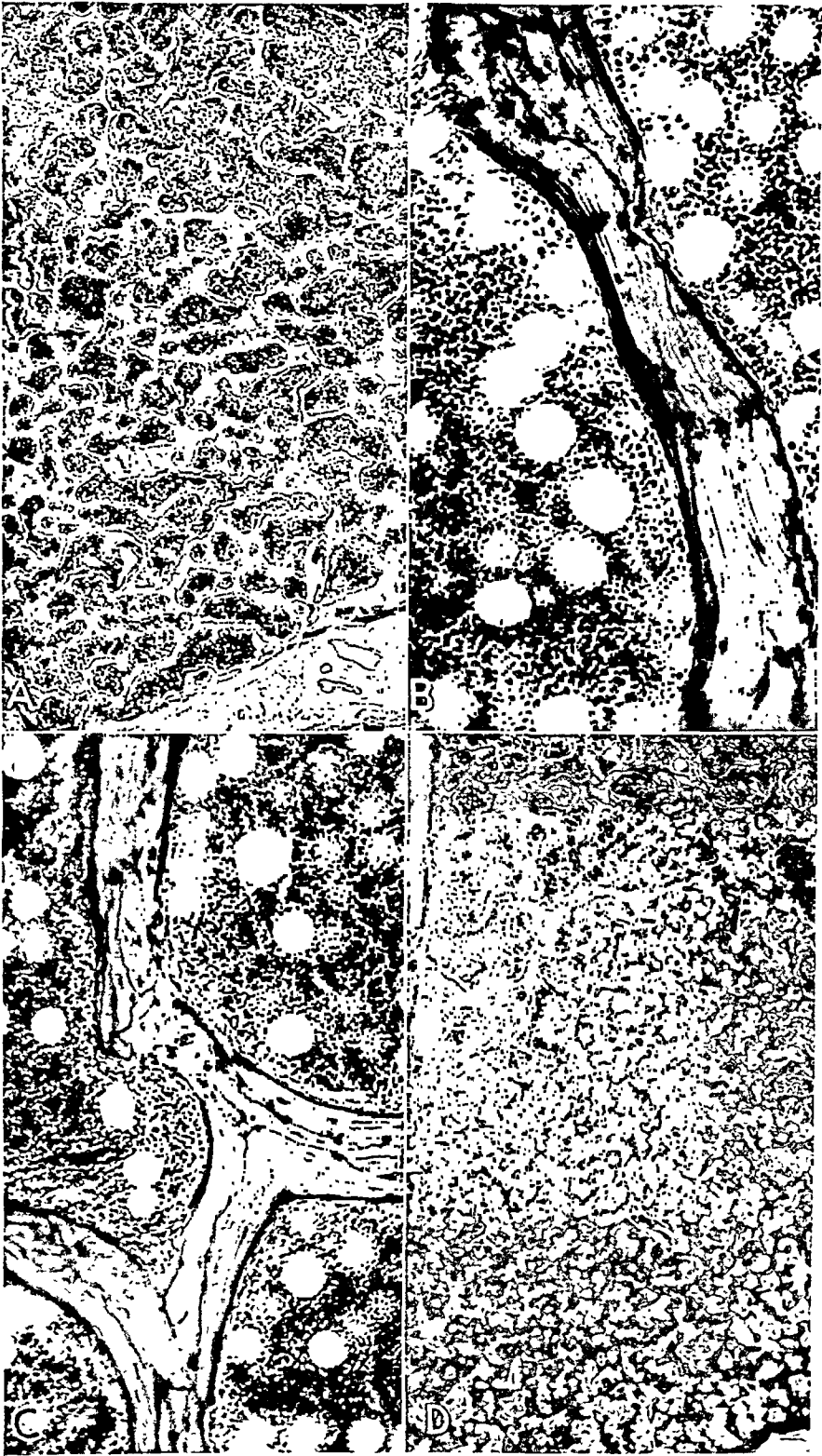


Figure 3

Fig. 3.—*A* shows a very low power survey of the anterior half of the body of the tenth dorsal vertebra. The general trabecular thickening is apparent, and the narrowed intertrabecular marrow spaces contain myeloid and fatty marrow; $\times 5$. *B* gives the architectural detail of one of the many trabeculae seen in *A*. The lamellar construction of the bone is illustrated. On the right above the middle, a Howship lacuna with osteoclasts is seen. Slightly below this, flattened osteoblasts are observed depositing new bone. Farther below, a fragment of newly formed bone, delimited by a cement line, appears on the surface of the trabecula. It is plain that there is no scarring or fibrosis of the myeloid marrow. The cement lines are irregularly directed; $\times 200$. In *C*, the trabeculae show still more changes in the minute architecture. Their composition of irregular fragments of bone, separated by thin cement lines, many of which are short, can plainly be seen. On the left, new deposition of bone is evident; resorption is in progress. To the right, some of the bone shows poor staining of the ground substance and few bone cells; $\times 135$. *D* is a low power survey of the posterior half of the first lumbar vertebra. It shows the dense area of sclerosis with a zone of thickened trabeculae still containing myeloid marrow above. The reconstruction of the trabecular architecture and the loosely cellular fiber marrow of the densely sclerotic patch are visible; $\times 5$.

tion defects were being filled out by new bone, such bone seemed to be deposited by flattened spindle-like osteoblasts; in other words, it was not a deposit of connective tissue new bone from the marrow. Often, one of the trabecular surfaces manifested resorption while the opposite surface was still smooth and regular, or this surface had a narrow zone of newly deposited bone. Furthermore, evidence of mild resorption and new bone formation was also to be observed on the walls of some of the haversian canals in thickened trabeculae. The histologic examination up to this point disclosed trabecular thickening to be the result of lamellar new bone deposition apparently following in the wake of initial resorption; it is necessary to acknowledge that the new deposition in order to cause trabecular thickening must be excessive or more than compensate for the resorption.

The other feature clearly evident is that there was no scarring or fibrosis of the myeloid marrow, although throughout the section none of the bony trabeculae appeared normal (fig. 3 *A* and *B*). When the depressions on the trabeculae that had resulted from resorption were examined, a few spindle cells were seen lining them. Close examination of the myeloid marrow in such a vicinity demonstrated that the small number of spindle connective tissue elements that appeared in conjunction with the resorptive process were derived from the endosteum. This endosteum normally sheathes and separates the myeloid marrow from the trabeculae. This fact is worthy of emphasis as it strikingly demonstrates that the changes of Paget's disease are not initiated primarily in the myeloid marrow, a point which Schmorl² emphasized.

On still closer microscopic inspection, one could not fail to notice that the minute architecture of these thickened trabeculae was everywhere abnormal (figs. 3 *B* and *C*). On the whole, whether considerably thickened or not, they were seen to be composed of numerous irregular fragments of lamellar bone, separated by relatively thin and short cement lines; these lines were much more numerous, more irregular and darker staining than the cement lines of normal spongy bone. (These thickened trabeculae were histologically different in appearance from the thickened trabeculae of the osteosclerosis that may be associated with myelogenous leukemia; in the latter, thickened trabeculae do not show such irregularities of cement lines, nor are they constructed of so many fragments of lamellar bone. From the foregoing facts the microscopic construction of the spongy trabeculae in this case forcibly suggested the mosaic architecture of Paget's disease, although nowhere in the section did it completely duplicate the appearance of the typical mosaic formations observed in florid Paget's disease.

It was also plainly discernible in the section that considerable bone within the substance of the thickest trabeculae had a peculiar appearance. In such areas, the bone cell lacunae were round or tended to be so; in places, this reached a striking degree. When it did so, it was apparently allied with distortion and disintegration of the canaliculi and bone cell processes, and with darker staining and granulation of the ground substance. There was likewise a loss of the lamellar arrangement in those areas showing the process in its most advanced stages. The fragments of bone most likely to present this appearance were those lying deepest within the substance of the thick trabeculae, although it could be seen on the surfaces of trabeculae, especially close to areas in the process of resorption. I have gained the impression that this is a regressive change, unrelated to the question concerning the blue-staining, primitive bone inclusions which are to be observed in the mosaic bone in florid cases of Paget's disease.⁹

9. The osteophytic overgrowths and the periphery of the vertebral bodies were composed of trabeculae of lamellar bone with fatty marrow between them. The trabeculae were thick and consisted of a large number of fragments.

2. In the gross (figs. 1 and 2), the first lumbar vertebra presented a patch of dense sclerosis in addition to sclerosis of the rest of its substance; on microscopic examination, several notable differences distinguished this zone of dense sclerosis from the tenth dorsal vertebra. Its dense sclerotic area retained no semblance of the original trabecular arrangement. Furthermore, the myeloid marrow had been practically completely replaced in this area by loosely cellular fiber marrow (fig. 3*D*). Higher power examination (fig. 4*A*) of this dense sclerotic area showed the absence of regular, normal formations of trabeculae. The original trabeculae had been completely replaced, and newly formed calcified bone was substituted for it. The bone here was everywhere in an active stage of reconstruction. On the whole, new deposition was rather excessive and the new bone, well calcified, was deposited in bizarre, grotesque or coral-like arrangements. The resorption was rather extensively established, particularly in the peripheral portions of the patch; where resorption was in progress, there were Howship's lacunae and osteoclasts. The new bone formation was through the medium of flattened osteoblasts; one of the striking elements in this regard was the very slight number of osteoid margins. When these were present, the overlying osteoblasts were taller. It was clearly evident that the newly deposited calcified bone was also rapidly resubjected to resorption, partly or wholly.

One of the notable features of this newly formed bone was that many of its component fragments showed numerous large and grouped nuclei, more reminiscent of the nuclear appearances of fiber than of lamellar bone. It appeared as a puzzling feature that baffled analysis. Although this bone suggested reticular fiber bone, it was not in any way connected by fibers with the fiber marrow, and it seemed definitely to be deposited by flattened osteoblasts. While lamellar construction of the ground substance was noticeable in places, in other places it was impossible to perceive such an arrangement. In the deposition of new bone, numerous small haversian canals were produced. One is therefore led to conclude that the newly formed bone in these sclerotic areas was quite calcified, deposited by osteoblasts, showing definite lamellar arrangement in parts; the portions not showing the lamellar arrangements were nevertheless more evolved bone. The cement lines were fairly numerous; some were thick; all were on the whole short; they were not so irregular, dark staining or numerous as those in typically formed Paget bone. This fact makes it evident that the bone resorption and deposition in this densely sclerotic area did not proceed at the rapid pace that it does in typical Paget's disease. Furthermore, the slowing of the process of new bone formation permitted calcification of the new bone which was reflected in the hardness and rigidity of the bones in this case.

The fiber marrow was composed of loose spindle connective tissue the cells of which were apparently connected by reticular processes. It contained a scattering of cells which included lymphocytes, plasma cells and mononuclear phagocytes. Within this fiber marrow, a few islands of myeloid and fatty marrow were still discernible; these islands were immediately surrounded by a layer of phagocytic cells of various thicknesses; the retained islands of myeloid marrow were being walled off and apparently crowded out in the course of the disease. Replacement of the myeloid marrow by fiber marrow was not the result of initial changes in the myeloid marrow. The fiber marrow was quite vascular in places, particularly so in the zones bordering the islands of retained myeloid marrow; occasional small amounts of fresh hemorrhage could be seen here. However, the fiber marrow contained neither the large quantities of blood pigment nor the numerous engorged vessels so common in the fiber marrow of Paget bone.

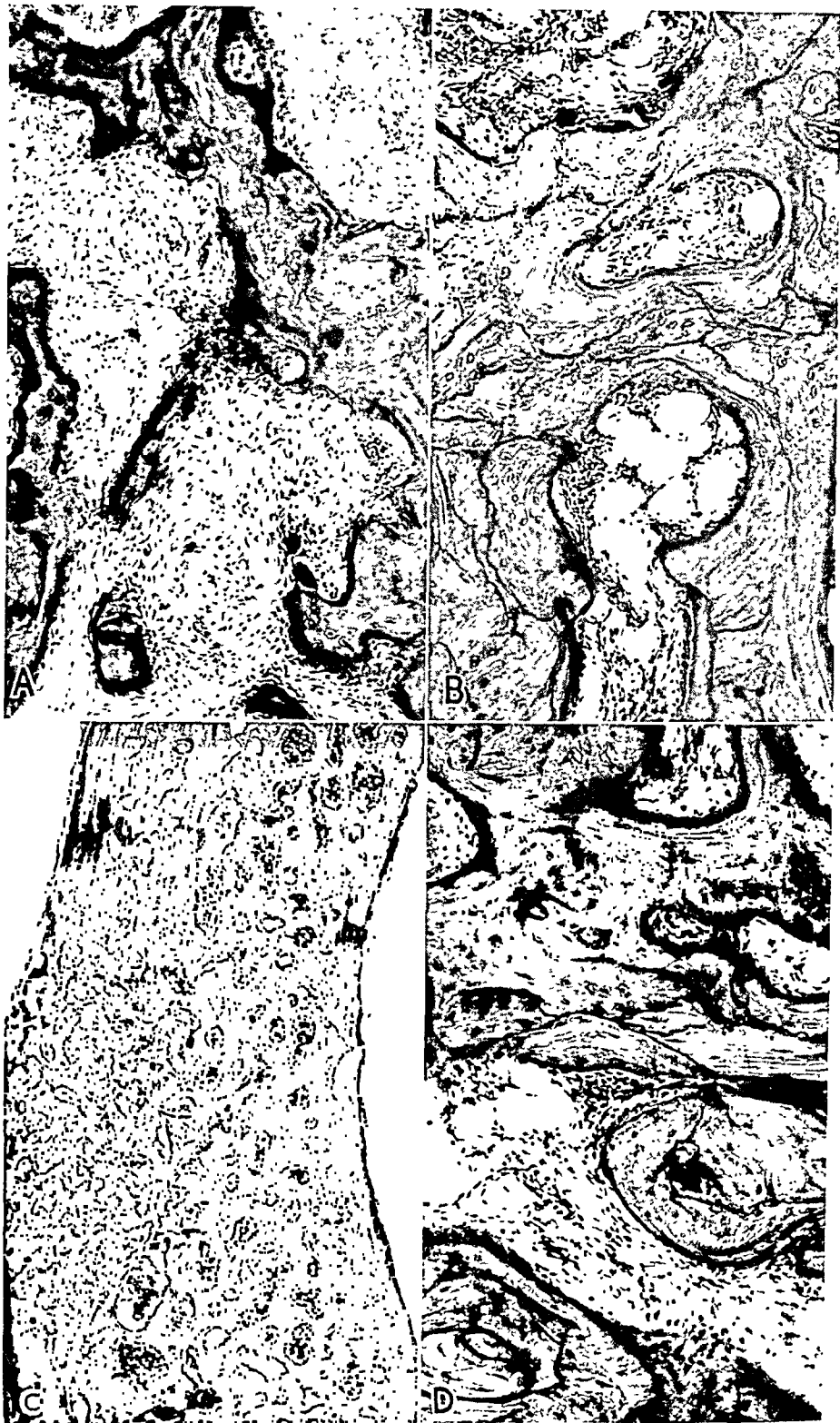


Figure 4

Fig. 4.—*A* shows the bone and fiber marrow, typical of the densely sclerotic area in the first lumbar vertebra. The new bone is calcified, and flattened osteoblasts are observed on many of the new trabecular surfaces; osteoid margins are not prominent. Resorption is also apparent. The new bone depositions are of irregular shape. The lamellar nature of this new bone is not very clear, except in an occasional area. The cement lines are on the whole short and irregular; some are thick. The fiber marrow is composed of loose, spindle, connective tissue; $\times 135$. *B* shows thickened trabeculae in the sacrum. They are composed of numerous fragments of bone, separated by thin and somewhat irregular cement lines. Most of this bone is clearly lamellar. The surface of some of the trabeculae show the deposition of new bone; $\times 135$. In *C* is the parietal bone, showing diffuse osteosclerosis, with the focus of transformed calvarial bones in the left middle region. The marrow here is fibrous and the enlarged spaces are open to beneath the pericranium; $\times 5$. *D* shows thick trabeculae within the transformed area illustrated in *C*. These are composed of fragments of newly formed bone; most of them are definitely lamellar. The cement lines are numerous fairly thick and somewhat irregular; $\times 135$.

Thus, the densely sclerotic area showed, as described, fiber marrow and completely transformed bone; the more simply sclerotic area adjacent to it revealed myeloid and fatty marrow with thickened trabeculae of definite lamellar construction. In the transition zone, some trabeculae had myeloid marrow on one surface, which was rather smooth, and fiber marrow on its opposite surface, which was markedly irregular. These transition trabeculae indicated the essential cause of differences between the densely sclerotic and the simply sclerotic bone. It is to be related to more rapid resorption associated with more excessive deposition of bone. The trabeculae, surrounded by myeloid marrow, near the densely sclerotic area, showed quite active resorption and deposition on their surfaces, but their reconstruction was not complete. The trabeculae farthest from the densely sclerotic area demonstrated considerable new deposition of lamellar bone and a marked increase of the cement lines (fig. 3 C), but these were not as irregular as those in the trabeculae adjacent to the densely sclerosed area.

3. Microscopic examination of the proximal sacral segment, which in the gross was densely sclerotic almost entirely, revealed practically all of the histologic features so far described in the tenth dorsal and first lumbar vertebrae. Most of the sclerotic area containing fiber marrow extended from the middle of the upper intervertebral disk into the substance of the segment. A very small patch with fiber marrow was also located posteriorly and inferiorly in this sacral segment. Most of the inferior, a good portion of the superior, the anterior and the posterior borders of this sacral segment were constituted of extraordinarily thickened trabeculae between which lay myeloid and fatty marrow. These extremely thickened trabeculae (fig. 4 B) above the middle of the lower disk were composed of lamellar bone; they were divided into numerous fragments by thin and somewhat irregularly directed cement lines. The lacunae of the cells within many of the component fragments were large and round. However, most of this bone was quite clearly lamellar bone. The surfaces of some of these trabeculae showed evidences of active resorption with osteoclasts in Howship's lacunae, as well as lamellar new bone deposition. The major marrow between these thickened trabeculae was myeloid and fatty. The more sclerosed area containing fiber marrow was like the analogous area in the first lumbar vertebra—in a stage of much more active transformation. The completely transformed trabeculae showed the tendency to mosaic architecture. No extensive primitive reticular bone formation was seen in the osteoblastic fiber marrow.

Sternum and Ribs: The sternum was involved by generalized simple sclerosis. On sagittal section its surface showed the same type of lesion as that described for the ninth dorsal vertebra (fig. 5). The closely set trabeculae extended from the inner to the outer cortical surface. This type of involvement was, of course, strikingly different from the appearance of the sternum involved by the more typical polyostotic Paget's disease, in which thick, condensed and pumice-like trabeculae frame the margins of the body and manubrium. A number of ribs were also studied. Outwardly, they had no appearance of abnormality. When sectioned sagittally, however, the marrow spaces were narrowed; although the cortices were not unusually thickened, they were quite compact; the trabeculae were thickened. On microscopic study, these thickened trabeculae were surrounded by normal-appearing myeloid and fatty marrow; they showed narrow margins of newly deposited bone in various places and, simultaneously, slight but definite evidences of active resorption. The thin cement lines were numerous and quite irregular in direction. An occasional vessel canal of the cortex contained fiber marrow, while subperiosteally there were slight resorption and new bone formation. In none of the sections examined was there evidence of scarring of the

myeloid marrow. The costal cartilages were calcified and in places manifested central ossification and subperichondrial ossification. The bone trabeculae within the substance of the costal cartilages and underneath the perichondrium were fairly thick and demonstrated an abundance of cement lines.

Calvarium: Gross appearance. The part taken for study composed the greater part of the frontal and occipital bones, both parietals, portions of the squamae of the temporals and parts of the great wings of the sphenoids. Its outer surface was fairly smooth; its shape, when viewed from above, was more or less oval, and the conformation was regular. All of its component bones were firmly synostosed. On the outer surface, remains of the coronal suture, extremely serrated, and the remains of a markedly serrated sagittal suture were still to be seen. The sphenofrontal and squamosal sutures were completely obliterated. The condition of the lambdoidal suture cannot be recorded as that section of the calvarium was not retained after parts had been taken for histologic study.

The inner surface of the skull cap did not present prominent depressions or furrows (fig. 6*A*); the depression for the convolutions of the cerebrum and the

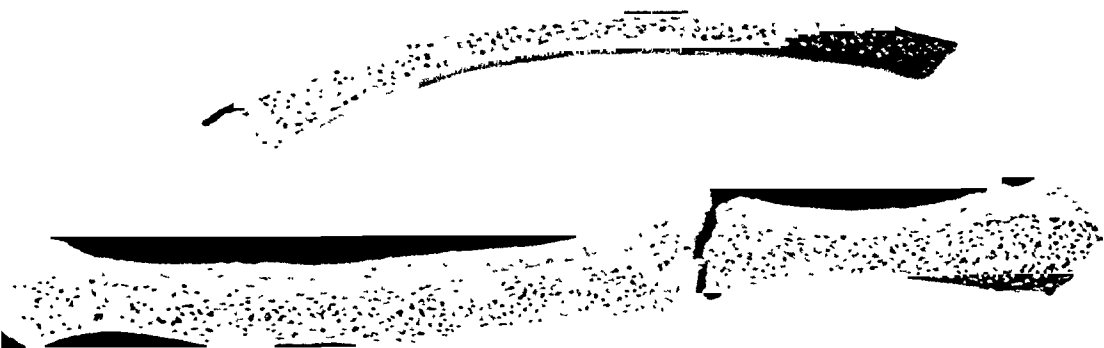


Fig. 5.—A rib and the manubrium and body of the sternum, in sagittal section. The diffuse osteosclerosis, owing to densely set, thick trabeculae, is obvious.

furrows for the lodgment of branches of the meningeal vessels were not as deep as might have been expected. Nor was there present, except in the very front of the calvarium, a longitudinal groove for the lodgment of the superior sagittal sinus. Furthermore, no prominent depressions for the arachnoid granulations were to be observed. Only the faintest traces of the coronal and sagittal sutures were seen on the inner calvarial surface.

Two centimeters behind the coronal suture, in the midline (fig. 6*A*), the calvarium revealed a thickness of 6 mm.; at other points from the midline of the frontal section, the thickness was as much as 8 mm. At 6 cm. behind the coronal suture in the midline, the thickness through the central portions of the parietal bone measured 9 mm. The squamae of the temporal bones measured between 3.5 and 6 mm. in thickness. The frontal bone, slightly anterior to the frontal eminences, measured between 3.5 and 5 mm. No portion of the calvarium exceeded 9 mm., although in many places it was thinner.

Gross examination exhibited a diploic structure everywhere, tending toward obliteration (fig. 6*A*); in places it had practically disappeared. Where it had, the bone was extremely compact; on the whole, these regions were thinner than those

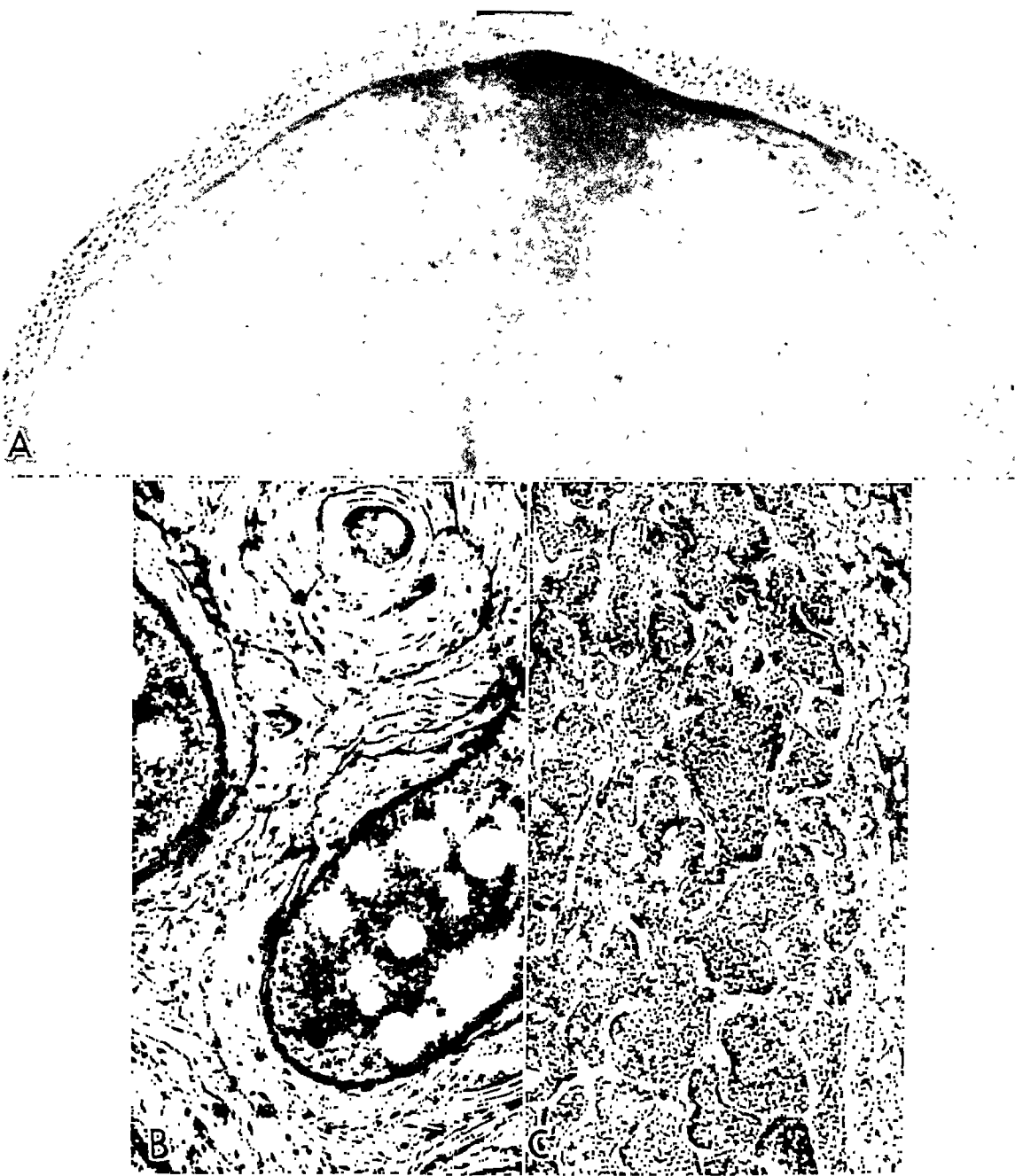


Fig. 6.—*A*, frontal section through the calvarium, 2 cm. behind the coronal suture in the midline. The tendency to obliteration of the diploe can be seen. The inner surface of the skull cap does not present any prominent depressions or furrows. On the whole, the outer table is thicker than the inner table. *B*, thickened trabeculae with diploic spaces, containing myeloid and fatty marrow. These trabeculae are from the nontransformed portion of the parietal bone. These thickened trabeculae plainly evidence the deposition of new bone which is present in the form of small fragments (breccie) separated by thin cement lines; $\times 135$. *C*, a portion of the ilium through the anterior half. It shows a cortical layer on the right, composed of compact lamellar bone with haversian systems. The marrow between the thickened trabeculae is myeloid and fatty; $\times 5$.

retaining diploic structure. Such obliteration was observed in portions of the frontal bone and even in the parietal bone close to the sagittal structure. Where the diploe were present, it was seen that the spaces were markedly reduced in size, and that the trabeculae were extraordinarily thick and closely set. With regard to the outer and inner tables, it is rather difficult to state precisely details concerning their gross features; in the compact areas no distinct tables could be observed; in the more diploic areas distinct table development was seen. Where distinctions between the tables were clearly manifest, the outer table seemed generally thicker than the inner table (fig. 6A). It was evident on gross examination that the portion of the calvarium studied was noticeably heavier than ordinarily; its increase in weight was quite apparently attributable to increased compactness rather than to any appreciable increase in thickness.

Microscopic appearance. A number of sections from various parts of the calvarium were examined histologically; all plainly demonstrated, as had been suggested by the gross appearance, that there was a condensing or osteosclerotic process in progress; it was akin to the sclerosing process observed in the other bones.

A section, which included a portion of the parietal and a fragment of the squama of the temporal bone, showed a distinct middle diploic zone composed of large and small spaces separated by thick bony walls. The diploic zone encroached on the inner table, but the outer table was quite prominent and thick. The surface of the outer table was covered by a thick layer of ground lamellae between which were thick appositional cement lines (*Ansatzlinie* of von K  lliker); very superficially, these appositional cement lines were so numerous as to give the section in this region a blue appearance. The outer surface of the outer table therefore showed evidence of slow and halting new bone deposition; in this section, there was practically no indication of resorption on the outer surface of the table. The outer ground lamellae, with their interposed, appositional cement lines, extended deeply into the substance of the outer table, but were disrupted by a fairly considerable number of thick-walled haversian systems with thick peripheral cement lines. These haversian systems were composed of lamellar bone with nuclei that stained well, but from the appearance of their cement lines they gave indubitable evidence of active reconstruction. The deeper portion of this table was composed of disrupted fragments of ground lamellae situated between haversian systems; added to these were some disrupted fragments of haversian systems. Much of this interstitial bone showed poor staining of the nuclei or complete absence of nuclear staining; portions also showed poor staining of the ground substance. Apparently, therefore, much of this bone was dead or dying. A number of the haversian canals of the outer table were filled with fiber marrow and, as stated, definite evidences of active resorption were visible on their walls.

Some of the diploic spaces contained fatty marrow; most of them still contained myeloid and fatty marrow. Their trabeculae were quite thick; some contained haversian spaces. The thickening of the trabecular walls (as elsewhere in the bones) can definitely be ascribed to the result of active new bone deposition on their surfaces following resorption. Practically everywhere on the surface of the trabeculae, resorption and deposition were in progress. The process seemed to be fairly active, though slow, without participation of the myeloid marrow. The thickened trabecular walls were built up of numerous small fragments of lamellar bone, irregularly arranged. The numerous interposing cement lines were on the whole thin, only a few being somewhat thickened but not abnormally. The nuclei of the more deeply placed lamellar bone of these trabeculae were likely to stain poorly.

The inner table was not unusually prominent, being reduced for the most part at the expense of the diploe. It contained only a few haversian systems. The innermost surface of the inner table was lined by inner ground lamellae with a few appositional cement lines. The number of inner ground lamellae was noticeably less than on the outer surface of this section. Other sections from the parietal bone essentially duplicated the appearances described.

However, one of the sections presented a rather distinctive aspect; this section, from the parietal bone farther posteriorly, included the obliterating sagittal suture and a portion of the other parietal bone. Its greatest thickness was about 9 mm. It retained a diploic structure, but the diploe were narrow, and the trabeculae were thick. Microscopic study revealed a portion of the bone included in this section as strikingly different from the rest of the section and from any of the appearances so far described in the calvarium (fig. 4 *C*). Here, the section showed that the bone had undergone an extensive architectural transformation. It appeared quite evident that within this area there had been extensive resorption with new bone formation and reconstruction on the walls of the diploic and haversian spaces. Haversian spaces opened beneath the pericranium; these spaces were filled with fiber marrow and were lined by new bone with large nuclei. The thick trabeculae within this focus were observed to be composed of fragments of newly formed bone, most of them definitely lamellar in structure, although some showed very large nuclei. The cement lines between these fragments were fairly thick and somewhat irregular (fig. 4 *D*). At the periphery of this portion of active transformation, evidences of resorption with osteoclasts were seen.

The active transformation had extended from the outer surface to about the middle of the bone (fig. 4 *C*). The rest of the section, although presenting no area of complete transformation, displayed exceedingly thick trabeculae in the process of much slower resorption and new bone deposition (fig. 6 *B*). Practically all of the haversian systems were bordered by scalloped cement lines. In the less severely transformed area, the diploic spaces contained myeloid and fatty marrow. On the inner surface, the inner ground lamellae were not particularly numerous, while on the outer surface these lamellae were thicker. Thus, this section illustrated a much more intense sclerosis than the one described; it was remarkable in that it presented an area of complete transformation.

Three sections taken from the most compact portions of the calvarium, that is, from the portions showing little if any diploic structure, demonstrated several special features. The compactness had resulted from obliteration of the diploic spaces by new deposits on their walls; the number of haversian systems below the inner and outer ground lamellae had increased considerably; part of the compactness was contributed by new depositions of inner and outer ground lamellae, in most places more prominent on the outer than on the inner side. One of these sections, it is to be pointed out, was from the squama of the temporal bone, which normally tends to show obliteration of the diploic structure. In regard to this bone, the condition was therefore nothing more than an exaggeration of the normal.

In recapitulation, the calvarium evinced several noteworthy features. Although it was, at the most, but slightly thickened, it was much heavier than normal. There was a progressive osteosclerosis in every way similar to the process occurring in the rest of the skeleton. The osteosclerosis was on the whole not associated with scarring of the myeloid marrow. There was deposition of lamellar bone in small irregular fragments; this was the cause of the trabecular thickening.

Furthermore, there was a definite tendency to deposition of new inner and outer ground lamellae; more of the outer ground lamellae was deposited, with apparent cessation of normal resorption on the outer surface of the calvarium. A focus of complete transformation and new bone deposition, associated with the appearance of some fiber marrow, was observed in one of the sections of the parietal bone; this was the only Paget-like focus seen in any of the calvarial sections.¹⁰

The question naturally arises, How do these calvarial bones differ from the normal? This, of course, presupposes that there are definite standards for the normal calvarium of a man 58 years of age; there are fewer data on the subject than could be desired. One of the chief sources of impediment in making comparisons is the considerable variation even within the so-called normal range. Owing to such variations, precise information on the thickness of the different parts of the calvarium, the thickness of the diploic zone and the appearance of the trabeculae, as well as the appearance and thickness of the inner and outer tables, is lacking. Generally speaking, the calvarial bones reach their full thickness during middle adult life, after which they may normally become somewhat thinner or even thicker. The calvarial thickness of 9 mm. in the case reported is not to be considered extraordinary for a man 58 years of age, as the upper limits of normal are not much shy of this figure. The character of the diploic zone in old age may vary; the diploe may be very extensive and range from plate to plate (this being more common), or they may be considerably reduced in size owing to obliteration (so-called senile osteosclerosis). Bernstein,¹¹ in a recent study of the normal histologic appearance of the calvarium (which I saw in manuscript), pointed out that in the 51 to 89 year age group there generally is expansion of the diploic zone at the expense of the inner and outer tables, but more largely of the inner table. He further asserted that in this age group the inner

10. The changes observed in the calvarium were different from the calvarial involvement of typical Paget's disease. In such involvement the bones are usually diffusely and uniformly implicated; they may be quite thickened; the occipital bone is likely to be more thickened than the rest. Partial Paget transformation limited to one or more bones of the calvarium is unusual, while a scattered and spotty type had been observed only once by Schmorl.² In that instance, the calvarium was not thickened, but numerous circumscribed, somewhat dark, lentil to penny sized foci were observed extending from the outer to the inner surfaces of the calvarium; these showed Paget bone microscopically. The unusual appearance of the calvarium in Pines' case³ is worthy of mention here as it did not suggest any appearance of Paget's disease either grossly or roentgenographically; it rather suggested Recklinghausen's disease. As regards the Paget nature of the calvarial changes in the case reported, they were the very antithesis of those manifested in Pines' case; they showed generalized sclerosis, rather than porosity.

11. Bernstein, S. A.: *Virchows Arch. f. path. Anat.*, to be published.

ground lamellae are usually much more numerous than the outer ground lamellae. Mair¹² also emphasized the predominance of the inner ground lamellae over the outer ground lamellae in later life. He even denied the possibility that resorption on the inner surface of the inner table occurred except rarely.

It is therefore worthy of note that the sections of the calvarium in the case reported showed, on the whole, a much greater deposition of ground lamellae on the outer surface than on the inner. Furthermore, where the diploic structure existed, the trabeculae were thick, the result of new bone deposition, and, finally, the significant abnormality resides in the construction of the thickened trabeculae by many frag-



Fig. 7.—The iliac bone, about 6 cm. above the upper margin of the acetabulum. The dense sclerosis behind the sacro-iliac joint is observed on the right. The thick trabeculae are evident in the anterior half, to the left.

ments of lamellar bone. The focus of more complete transformation marks the basic nature of the calvarial osteosclerosis.

Innominate Bones: Both of these bones were examined; they were heavier than normal, all prominences being exaggerated; certain portions seemed enlarged. The inner architecture was studied in the gross, by longitudinal sectioning through the acetabulum and horizontal sectioning through the iliac portions. This examination disclosed trabeculae thickened everywhere, with areas of intense sclerosis in the iliac bones behind the sacral articulations. There was a considerable deviation from the normal throughout. The cartilage in the acetabula was degenerated; the attached synovia showed moderate hypertrophy. A horizontal segment was removed from one of the iliac bones, about 6 cm. above the margin of the acetabulum (fig. 7). In the microscopic sections prepared therefrom, all

12. Mair, R.: *Ztschr. f. mikr.-anat. Forsch.* 5:625, 1926; *Ztschr. f. Anat. u. Entwicklungsgesch.* 90:293, 1929.

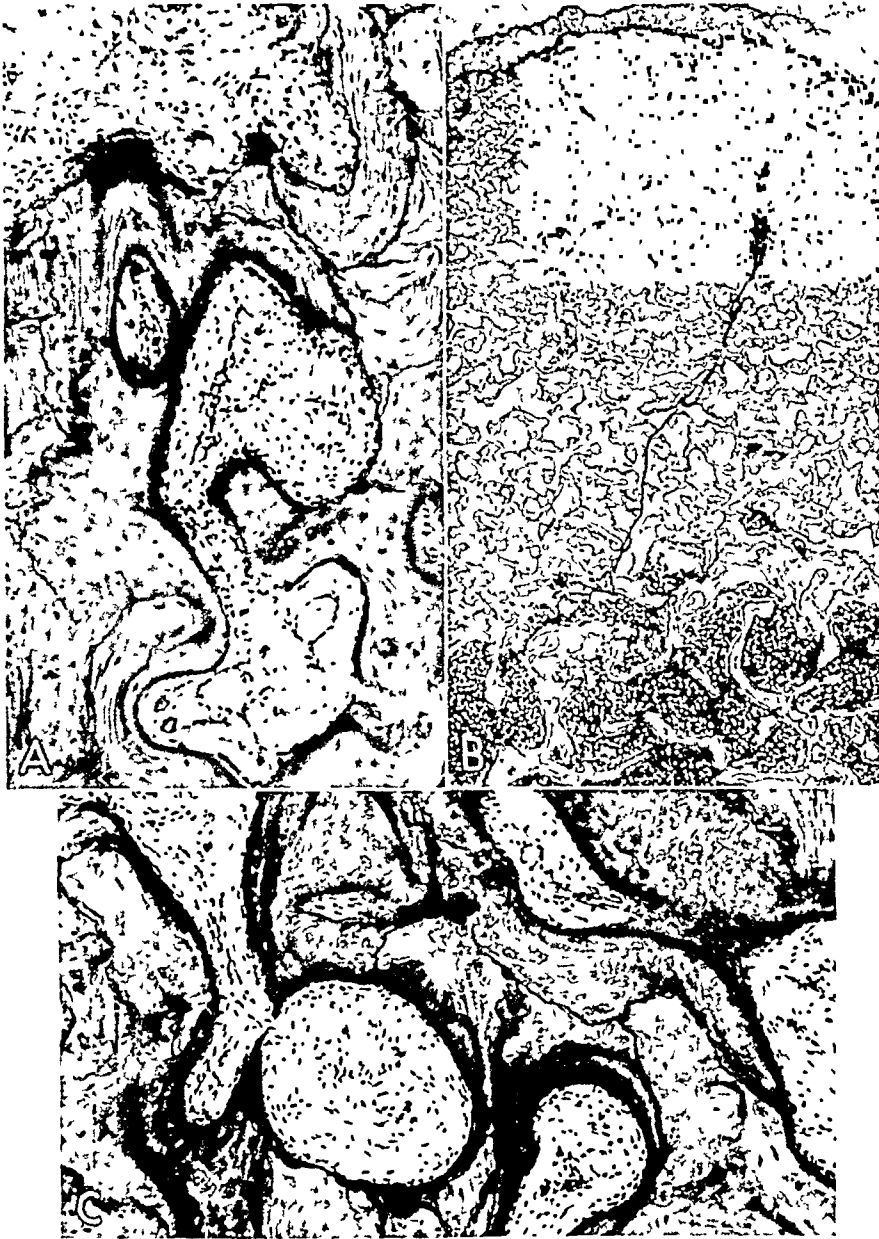


Fig. 8—*A*, enlarged haversian spaces in the cortical layer of the bone shown in figure 6 *C*. The enlarged spaces contain fiber marrow; new bone deposition is seen on the walls of some of these spaces. Resorption with osteoclasts is observed in other spaces; $\times 135$. *B*, an area below the articular cartilage of the sacral articulation, showing the fiber marrow and newly formed bone in the area of dense sclerosis shown in figure 7; $\times 5$. *C*, the higher power appearance of the bone in the densely sclerotic area shown in *B*. The construction of these newly formed trabeculae of fragments of lamellar bone, separated by thick and short cement lines, gives the appearance of almost typical Paget bone; $\times 135$.

degrees of pathologic change so far described in the various bones of the skeleton were seen concentrated even more intensively.

Sections from the more anterior portions, presenting an outer and an inner cortical layer, showed them to be composed of very compact lamellar bone, with haversian systems extending, in many places, to immediately beneath the periosteum (fig. 6C). At one or two points, subperiosteal resorption was observed, but, generally, the striking absence of periosteal activity and periosteal new bone deposition was manifest. Within these cortical layers, a number of haversian canals were greatly enlarged; these canals contained fiber marrow. Some had irregular walls and numerous osteoclasts; others showed definite evidence of new bone deposition, by osteoblasts (fig. 8A). The trabeculae throughout, however, were thickened, there being active resorption and new bone deposition. Although these trabeculae were thickened, the marrow was myeloid and fatty where the original trabecular structure was retained (fig. 6C).

Somewhat more posteriorly, a section showed much more extensive resorption of the cortex with enlargement and confluence of the haversian systems. The large, confluent haversian spaces were filled with fiber marrow; new depositions on the walls of these spaces could be seen. Although deposited by osteoblasts, this new bone appeared immature and almost identical with fiber bone. The marrow between the thickened trabeculae remained myeloid and fatty. Still more posteriorly, the process as observed in the outer cortex was much more pronounced, and very few of the original haversian systems remained. The depositions of new bone tended to create a Paget-like, mosaic architecture, which reached the typical appearance in the very dense, sclerotic bone observed under the cartilage behind the sacrum (fig. 8B and C). Some of the marrow between the trabeculae was still myeloid and fatty. In this section, a focus of blue-staining, primitive-appearing bone was seen; it seemed to be hypercalcified bone, in other respects similar to much of the rest of the bone deposited in Paget's disease, when the new depositions are active. About some of the trabeculae, there were wide zones of cells separating the trabeculae from the myeloid and fatty marrow; these cells were fused with the rest of the marrow; they seemed to be modified marrow cells containing no interspersed fat.

COMMENT

In the histologic descriptions, consistent emphasis was laid on certain appearances of the nature of Paget's disease. In the description of the thickened but unreconstructed trabeculae, it was indicated that they presented increased cement lines and were composed of an increased number of fragments (*breccie*) of lamellar bone; on the surfaces of such trabeculae, evidence of resorption and new bone deposition was plainly apparent, although the intervening marrow remained myeloid and fatty. In the locations (areas of dense sclerosis) where the process was apparently much more florid, the myeloid marrow was replaced by fiber marrow and the original bone was replaced by new bone. This new bone was deposited by osteoblasts, was well calcified, was definitely lamellar in part only and contained cement lines, some of which were thick and irregular. Thus, the specialized histologic appearance of the bones in this case was highly suggestive of, without being exactly analogous to, the typical mosaic formation observed in florid Paget's disease.

In the introductory portion of this article, the mosaic architecture that typifies so-called Paget bone was described in some detail; that description pertained to the appearance of the newly formed lamellar bone in the distinctly florid stage of the evolution of the disease. However, the mosaic appearance (on which the histologic diagnosis of Paget's disease depends) is capable of wide variation. The mosaic is most typically constructed in areas of most active disease. The great tendency for spontaneous healing in Paget's disease is associated with regression of the mosaic from the typical. In classic polyostotic Paget's disease, the typical mosaic is to be observed in some bones or in portions of some bones, while healing with regression of the mosaics can be seen in other bones or in other portions of a bone showing florid Paget's disease. Furthermore, when investigation of many bones in a case of polyostotic Paget's disease is made, it may be observed that Paget's disease is capable of evolving more slowly in certain bones. The appearance of extensive mosaic architecture is not evident in any of the bone diseases except Paget's disease. The more florid the disease, the more chaotically are the new lamellar bone fragments arranged, and the more typical the mosaic architecture. Conversely, the more slowly progressive the disease, the more regularly arranged do the new lamellar bone fragments appear, and therefore the less chaotic the mosaic structure. Even in the most florid areas of the disease, the mosaic appearance is to be interpreted as evidence of the initiation of the healing process.

The slow evolution of the pathologic changes in the case reported is the reason for the absence everywhere of a mosaic arrangement such as appears in typically florid areas of Paget's disease. Thus, the slow progress of the disease permitted healing to keep almost apace with its march. For this reason, the cement lines, although more numerous, were on the whole fairly thin and not very irregular; this produced a mosaic architecture not altogether typical compared with that expected in florid disease foci. Even in the densely sclerotic areas, healing kept so close to the changes inaugurated by the disease process that the new bone was well calcified and its mosaic highly suggestive of, but not completely analogous to, that seen in florid disease foci. The slow progress of the evolution of the disease and the concomitant healing were furthermore the reasons why the typical gross appearance of Paget's disease did not manifest itself in this case. Therefore, this is an instance of distinct Paget's disease, peculiar in that slow progress of the pathologic changes permitted healing to keep almost abreast of the evolution of the disease.

The accepted concept of the gross and pathologic anatomy of Paget's disease has not heretofore included a clearcut description of a

form such as this, simulating osteosclerosis. M. B. Schmidt¹³ described an apparently similar condition, which he interpreted as osteosclerotic anemia. His subject was a man, aged 56, who had splenomegaly and an anemia that was never definitely classified. During life, he had received radiation therapy for the reduction of an enlarged liver and spleen. The bones showed osteosclerosis (due to new bone deposition on the existing bone and replacement of the myeloid marrow by fiber marrow to the extent of less than one-half). Schmidt stated that the new bone depositions were the result of osteoblastic activity, that osteoclasts were well nigh absent, that the typical mosaic of Paget's disease was not present, and that there were no gross deformities of the bones. He was able to examine the lower half of one femur, and found that while the cortex was not enlarged, the spongiosa was sclerotic and contained a focus of dense sclerosis measuring 2 by 1.5 cm. He was in a dilemma as to the interpretation that could be placed on these changes in the bones, and finally decided that whatever was causing the anemia was producing the changes observed both in the bone and in the marrow. He made it clear that he did not believe that the changes in the marrow were the cause of the anemia.

In searching the literature, Schmidt noted that his case resembled the second and third cases reported by Assmann.¹⁴ It is difficult to be certain of the exact similarity between the changes in the bones in Assmann's cases and in those described by Schmidt. In Assmann's important contribution, the presence of osteosclerosis with leukemia is established beyond doubt; where he discusses anemia and osteosclerosis, no clarity in the histologic descriptions of the changes in the bones exists. It seems to me that since Schmidt himself could not accept the view that the changes in the bones in his case were the result of anemia, and since the anemia was never clearly classified, it may be fair to assume that the anemia was a coincidental feature (the changes in the bones being entirely unrelated to the cause of the anemia). In the case reported here, a moderate secondary anemia existed at the time of the patient's admission to the hospital: there were no particular abnormalities in the red and white blood cells, and since evidences of renal insufficiency were present, sufficient reasons existed for the anemia. Nor did the myeloid marrow, where present (it was not much reduced in amount), appear to show abnormalities. There is no basis in this case for attributing the changes in the bones either to fibrosis of the marrow or to the cause inducing the secondary anemia.

Whether the changes in the bones described are related to the rare endosteal form of Paget's disease which Pick¹⁵ briefly mentioned in

13. Schmidt, M. B.: *Beitr. z. path. Anat. u. z. allg. Path.* **77**:158, 1927.

14. Assmann, H.: *Beitr. z. path. Anat. u. z. allg. Path.* **41**:565, 1907.

15. Pick, L.: *Klin. Wchnschr.* **2**:1044, 1923.

1923 is also difficult to determine. His student, Stenholm,¹⁶ elaborated somewhat more fully on this condition; the cases are listed as cases 11 and 12 in his monograph. Case 11 concerns a boy, 15 years of age, who had sclerotic patches in the tibia and in the fifth lumbar vertebra. In these sclerotic patches, new bone formation was in ascendancy, and osteoclasts were few. The marrow was not particularly congested, nor were there the numerous blood vessels and the large amounts of blood pigment that may be found in the fiber marrow in typical Paget's disease. Case 12 concerned a 17 year old girl. Stenholm concluded that the particular peculiarity of these cases was the atypical localization of the disease to the marrow cavity and the absence of change in form of tubular bones when involved. In 1926, Pick's former assistant, Christeller,¹⁷ in a symposium on fibrous osteodystrophy, again mentioned the endosteal form of Paget's disease. He also stated that in a tubular bone the peculiarity of this lesion is its localization to the marrow cavity, which is filled by a dense, white mass consisting of fibrous tissue and bony trabeculae; similarly, sclerotic foci are to be observed in the vertebrae. These microscopic features were interpreted as evidences of healing, but sufficient details were not given by Pick, Stenholm or Christeller to class these cases absolutely as Paget's disease. Furthermore, the fact that they occurred in young people may be the key to the considerable amount of healing found microscopically. If they are really instances of Paget's disease, the healing tendency may have modified the appearance from the more commonly recognizable manifestation of Paget's disease.

Two more points remain to be discussed: the rôle of chronic nephritis and uremia in influencing the changes in the bones, and the possible influence of lead poisoning (since the subject was a house painter) on these changes. Chronic nephritis is known (under certain circumstances) to induce resorption of bone, so that if it had any effect it was in the direction of increasing the resorption rather than the new depositions. While chronic lead poisoning in infants produces osteosclerosis at sites of most active growth of bone, in adults it appears to have no effect on the bone. Information on this point, however, is rather scant; it is known that in adult dogs chronic lead poisoning does not produce osteosclerosis, while it does so in puppies.

SUMMARY

Bones from a man 58 years of age, showing advanced osteoclerosis, markedly intense in certain areas, were studied. The calvarium, spine, innominate bones, sternum and ribs were investigated; the long tubular

16. Stenholm, T.: *Osteodystrophia fibrosa*, Uppsala, Almqvist & Wiksell, 1924.

17. Christeller, E.: *Verhandl. d. deutsch. path. Gesellsch.* **21**:7, 1926.

bones could not be examined. Although Paget's disease was nowhere plainly suggested in the gross, except possibly in the ilia, the microscopic studies led to the conclusion that the changes in the bones were those of Paget's disease. Even the histologic appearances were nowhere similar to the typical mosaic arrangement of florid Paget's disease. It was concluded that the slow evolution of the pathologic changes in the case recorded was the reason for the absence everywhere of a mosaic arrangement such as appears in typically florid areas of Paget's disease. The slow progress of the disease permitted healing to keep almost abreast with its evolution. Furthermore, the slow progress of the evolution of the disease and the concomitantly rapid healing led to the production of osteosclerosis rather than to the usual gross changes of Paget's disease. A somewhat similar case was described by Schmidt, but was erroneously interpreted as osteosclerotic anemia. The relation of this condition to Pick's endosteal Paget's disease is not clear. Thus, Paget's disease may appear in atypical form, the bones, in the gross, evidencing generalized osteosclerosis.

LEIOMYOSARCOMA OF THE DUODENUM

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Eighteen cases of leiomyosarcoma of the small intestine have been reported since 1875. In thirteen of these cases the exact site of origin was mentioned: in ten, the jejunum; in one, the ileum, and in one, the duodenum. It has seemed worth while to report the following case, since it is only the second known case in which the duodenum was involved.

REPORT OF A CASE

A Hungarian machinist, aged 37, was first seen in September, 1927, when he complained of having had tarry stools for seven weeks, and weakness, pallor and palpitations for three weeks. His family, past and personal history was irrelevant. His general health had been good. He appeared well developed, pale and chronically ill. Physical examination gave negative findings except for severe secondary anemia and stools which gave a 4+ response to the guaiac test. A blood count revealed 1,700,000 red blood corpuscles and 6,500 white blood corpuscles. The hemoglobin content was 35 per cent, and the reticulocytes comprised 8.4 per cent. Roentgenograms of the gastro-intestinal tract showed no evidence of a gastric or duodenal ulcer. However, a diagnosis of duodenal ulcer, hemorrhage and secondary anemia was made. The patient was put on a Sippy diet with the addition of liver.

On Sept. 14, 1932, he was readmitted to the hospital with the same complaints. In addition, he had lost weight and had eructations after meals and swelling of the legs and feet; during the previous eight days he had severe squeezing pains in the right leg. Five weeks before this he had first noticed a lump in the right side of the abdomen. He had neither abdominal pains nor fever. There was a moderately tender mass in the right upper quadrant of the abdomen which projected from 3 to 4 cm. below the margin of the liver. This mass was hard and irregular and seemed to be attached to retroperitoneal tissues. There were also a slight dulness at the base of the right lung, with occasional râles and diminished breath sounds, and a slightly enlarged heart, with a systolic blow at the apex. Pitting edema was present in both legs, but was more marked in the right leg.

A blood count showed: hemoglobin, 50 per cent; red blood corpuscles, 3,470,000, and white blood corpuscles, 4,900. The stools gave a negative reaction to the guaiac test. The Wassermann reaction was negative. The urine was normal. Roentgenograms of the colon and abdomen showed a large dense shadow in the right upper quadrant. It was thought that the increased density was due to an abdominal tumor pressing on the colon. The following diagnoses were considered: mesenteric tumor, retroperitoneal tumor and a new growth of the kidney.

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The patient complained of severe pain extending from the right knee downward. Four days after admission he had an attack of dizziness, fainting, palpitation and diaphoresis. Two days later, on September 20, he had a tarry stool; he passed at once into a state of severe shock, and died. The shock was thought to follow an extensive hemorrhage into the gastro-intestinal tract. The clinical diagnosis was: carcinoma of the colon secondary to polyposis (?), secondary anemia due to chronic and acute loss of blood, circulatory failure and shock due to massive hemorrhage into the intestine (probably the colon).

Autopsy.—Four hours after death autopsy was performed. The body was that of a well developed, well nourished, muscular white man, 167 cm. in length. The pupils were equal and regular and measured 6.5 mm. in diameter. The eyes, nose and ears appeared normal. The mouth was in good condition and the neck was normal. The thorax was well developed, with a costal angle of slightly over 90 degrees. The abdomen was flat except for a slight, firm, rounded swelling at the right of the umbilicus. There were no palpable lymph nodes in the inguinal or axillary regions. The extremities appeared normal.

The peritoneal cavity contained no free fluid and was free from infection. The small intestine was pushed into the left lower quadrant by a large, nodular, firm retroperitoneal mass, measuring 15 by 18 by 12 cm. This mass occupied the central portion of the abdomen, extending farther to the right than to the left. The bulk of it lay over and to the right of the upper lumbar vertebrae. The tumor involved the right and posterior aspects of the second portion of the duodenum and the posterior and inferior aspects of the third portion of the duodenum, both of which were pulled down to the level of the lower lumbar vertebrae. The anterior surfaces of the duodenum were free. The mass was also adherent to the lower pole of the right kidney, but there was no involvement of the liver, stomach, spleen, left kidney or suprarenals. The tumor reached to the posterior aspect of the head of the pancreas, but had not invaded its capsule. The colon curved over and around it, but was otherwise normal in appearance. When the duodenum was opened, two ulcerations were found in the region of tumor involvement: one was 8 cm. below the pylorus at the level of the papilla of Vater and measured 3 cm. in diameter; the other was 15 cm. below the pylorus and was a few millimeters in diameter. The margins of these ulcers were firm and irregular; they protruded above the tumor mass and appeared to be continuous with it. At the base the ulcers communicated with large cavities within the degenerated center of the tumor. The larger ulcer led to a cavity 13 cm. in depth, which extended in a diagonal course posteriorly to the right and downward. A section through the tumor showed a hollowed-out mass of tissue, the walls of which were nodular, fairly firm and pale gray. Much necrosis had occurred in the center of the individual nodules. The lumen was occupied by a small amount of thin tarry fluid. Though the mass was adherent to the capsule at the lower pole of the right kidney, it did not appear to involve the tissue of the kidney. It compressed the inferior vena cava, which was otherwise normal. A fairly fresh, firm thrombus occluded the left common iliac vein. The right iliac, femoral and external saphenous veins contained no thrombus. Occluding the right internal saphenous vein and its branches was a pale, friable thrombus, which appeared to be older than that in the left iliac vein.

There were a few fibrous adhesions in the right pleural cavity. The left pleural cavity and the pericardial cavity were normal. The heart weighed 380 Gm. and showed marked dilatation of the right auricle and ventricle and moderate sclerosis of the coronary arteries. The lungs were normal except for the presence

of large masses of thrombotic material in all the large branches of the coronary arteries. The spleen weighed 360 Gm. and was large, soft and deep red.

The liver weighed 2,650 Gm. and measured 30 by 19 by 9 cm. It contained five tumor nodules varying in diameter from 0.5 to 5 cm. They were pale and firm and were outlined by zones of red; the larger ones had soft centers. The bile passages were normal. The common duct extended over the surface of the tumor, but was not obstructed by it. The kidneys were somewhat enlarged. The right kidney was adherent to the tumor mass, but was not invaded by it. The lower portion of the right ureter was compressed by the tumor, with a consequent dilatation of the pelvis of the kidney and the ureter above that point. The pelvic organs were normal. The gastro-intestinal tract, except the portion already described, was normal, and, although the feces in the colon were tarry, there was no evidence of massive hemorrhage. The brain and cord were not removed.

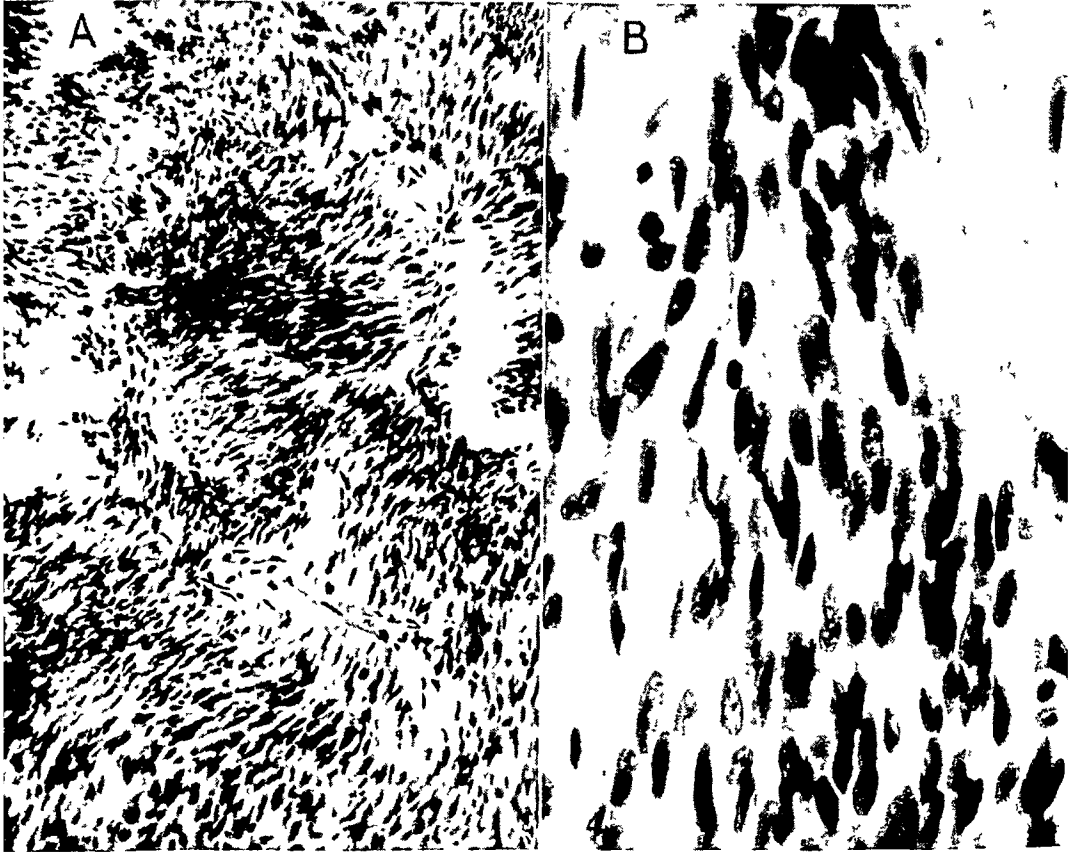
Microscopic Examination.—Section Through the Retroperitoneal Tumor Mass: The tissue consisted of interwoven strands and whorls of spindle cells arranged in irregular palisades and columns. The majority of the nuclei were vesicular and cigar-shaped, though some were pleomorphic and others were long dark-staining rods. Mitotic figures were rare. The intercellular substance was scanty. In places there were infiltrations of plasma cells, lymphocytes and occasional eosinophils. Blood vessels were few, and there were areas of necrosis. These contained extravasated blood, moderate numbers of polymorphonuclear cells and lymphocytes and several large phagocytes which were full of ingested material. The Foote-Bielschowsky stain showed a scanty reticulum, which sometimes surrounded individual cells.

Section Through the Large Duodenal Ulcer: The duodenal mucosa near the margin of the ulcers was edematous, congested and infiltrated with many lymphocytes, plasma cells and eosinophils. Nodules of tumor tissue had infiltrated the muscularis and submucosa. Outside the duodenum the tumor resembled that in the previous section in most places, but other areas were less cellular and had more intercellular collagen. The cells had more cytoplasm and showed much palisading. No capsule was found. There was much necrosis along the surface of the cavity, and numerous lymphocytes and plasma cells were present. A similar infiltration was found in some areas in the tumor tissue. Masson's trichrome stain showed dense collagen and few cells in some regions. Protoplasmic fibrillae could be distinguished in many tumor cells. The phosphotungstic acid stain revealed definite protoplasmic fibrillae in the tumor cells.

Nodules in the Liver: The scalloped margin was sharply defined, and cells resembling endothelial cells surrounded the mass but were separated from it by a sinus-like space containing a fine eosinophilic precipitate. There was no fibrous capsule. The tumor tissue resembled that already described except that it was more cellular and the cells were more rounded. There were areas of degeneration and infiltration by lymphocytes, plasma cells and eosinophils. The adjacent sinuses were engorged. The liver tissue elsewhere contained a moderate number of lymphocytes and polymorphonuclear leukocytes in the portal areas; there was some congestion in the central areas. The phosphotungstic acid stain and the Masson trichrome stain brought out protoplasmic fibrillae in the tumor cells. The Foote-Bielschowsky stain showed a delicate reticulum around each cell in one nodule, while in another nodule the reticulum was rather scanty, but in places surrounded individual cells.

Other Organs: The heart was normal, except for hypertrophy of the muscle fibers and congestion of the capillaries and venules. There was a small lipochrome

deposit at the poles of the nuclei. The aorta showed a slight arterioclerosis. The lungs showed fresh hemorrhages in many alveoli; these were unaccompanied by any inflammatory reaction in most places. A few alveoli contained small numbers of polymorphonuclears, lymphocytes and eosinophils. The alveolar walls were congested and infiltrated with monocytes, a few lymphocytes and occasional polymorphonuclear leukocytes. The bronchi contained fresh blood. There was moderate emphysema. The pulmonary artery was occluded by thrombotic material, a large portion of which appeared old; the remainder was homogeneous and resembled a propagated clot. The wall of the vessel was disrupted at the point of attachment of the thrombus. The vasa vasorum showed perivascular infiltration



Section from tumor mass: *A*, low magnification; *B*, high magnification.

of lymphocytes, polymorphonuclear cells and monocytes. The spleen presented signs of acute splenic tumor, with extensive hemorrhage into the pulp, congested sinuses and marked infiltration of inflammatory cells, chiefly plasma cells and eosinophils, and also many polymorphonuclears, lymphocytes and phagocytes. No pigment was found. Many fat vacuoles were surrounded by foreign body giant cells. Some of the latter contained ingested droplets of fat. The pancreas, suprarenals, kidneys and pelvic organs were normal. The left femoral vein contained thrombotic material, some of which was old, and some more recent and homogeneous. Organization had begun at one point. The right iliac vein contained no thrombus. Some of the intima lacked endothelial lining, and in this region all layers of the vessel wall seemed disorganized; budding capillaries and young fibroblasts were present, suggesting the beginning of organization of a thrombus.

The anatomic diagnosis was leiomyosarcoma of the duodenum, secondary leiomyosarcoma of the liver, compression of the inferior vena cava, thrombosis of the common iliac veins, pulmonary embolism on both the right and the left and arteriosclerosis of the coronary arteries.

In summary, the features of interest are: a history of duodenal ulcer in a middle-aged man, with repeated intestinal hemorrhages for five years before death; a mass in the right flank, which was first noted only six weeks before death; the finding at autopsy of a large sarcomatous retroperitoneal tumor intimately incorporated in the duodenal wall and ulcerating into the lumen; metastasis to the liver, and a histologic structure of leiomyosarcoma. It is probable that the thrombosis of the common iliac vein was secondary to the compression of the inferior vena cava by the tumor, and the disrupted architecture of the wall of the right iliac vein leads one to suspect that the thrombotic material plugging the pulmonary arteries was originally situated in this vessel. Death followed pulmonary embolism involving all the main branches of both pulmonary arteries.

COMMENT

The only case of leiomyosarcoma of the duodenum in the literature between 1875 and 1933 is that reported by von Salis,¹ in 1920.

In a man, aged 40, the onset was seven years before death. The symptoms were fever, a mass in the abdomen, three fingerbreadths to the left of the umbilicus, and obstipation. There was neither vomiting nor bloody stools. An operation, not described, was performed, which was followed by recovery. Three years after the onset a second operation was performed. The wound drained large amounts of purulent material. During the remaining four years the patient had occasional attacks of fever and diarrhea, which were associated with inadequate drainage from the wound. Another laparotomy was performed, and a large tumor mass was found, into which the fistula opened. There was also a fistulous opening between the drainage tract and the small intestine. The patient survived the operation about four months.

Autopsy disclosed a mass the size of a baby's head attached to the duodenum just above the duodenojejunal junction. It was adherent to the adjacent organs and contained a complicated system of cavities opening into the duodenum and also through the abdominal wound. The cavities contained thick pus and had thick walls. The tumor was lobulated, grayish red and soft in the center. The peritoneal cavity contained 2,500 cc. of thick purulent material, and there was an abscess in the liver. Microscopically, the tumor was composed of spindle-shaped cells. No mitoses were found. The similarity to our case is striking in regard to the age of the patient, the duration of the symptoms, the size of the tumor and the histologic structure.

A third case, that reported by Hüllt,² might perhaps be included.

A woman, aged 72, had symptoms for several years. An operation was performed, and the patient died two days later. A large tumor was found, which was

1. von Salis, H. W.: *Deutsche Ztschr. f. Chir.* **160**:180, 1920.

2. Hüllt, H.: *Deutsche med. Wchnschr.* **32**:944, 1906.

thought to have its origin in the muscularis of the duodenum. The tumor infiltrated the pancreas. There was no metastasis. A diagnosis of myoma of the duodenum was made.

From a study of the literature it is evident that leiomyosarcoma of the gastro-intestinal tract is uncommon. According to Corner and Fairbank,³ the ratio of incidence of myosarcoma of other types in the stomach is 6:52, for the small intestine it is 2:63. According to Speese,⁴ this ratio for the small intestine is 1:96. The criteria for the diagnosis of leiomyosarcoma are difficult to apply, since in most cases no special stains were used to establish the presence of myofibrillae and prove the muscle fiber origin, and the malignant nature of the tumors has not always been clearly demonstrated. The diagnosis of malignancy depends largely on the histologic appearance, as the tumors metastasized in only four of the nineteen cases, or 21 per cent, and the tumors tend to grow in bulk in their original site rather than to invade adjacent tissues extensively. Most, however, are not encapsulated. We believe that the diagnosis may be accepted in the cases of Babes and Nanu,⁵ Bonneau,⁶ Cabot,⁷ Cattell and Woodbridge,⁸ Demmin,⁹ Egtermeyer,¹⁰ Ghon and Hintz,¹¹ Glass and Alsberg,¹² Kathe,¹³ Marwedel,¹⁴ Morpurgo,¹⁵ Richter,¹⁶ Rieckenberg,¹⁷ Steiner¹⁸ and Wortmann.¹⁹

The incidence of leiomyosarcoma of the small intestine, as shown by the accompanying table, is greatest between the thirtieth and fiftieth year.

Of the eighteen patients whose sex was specified, twelve were men. In the majority of cases the symptoms lasted for from six to twelve months. However, in a case reported by Demmin, no symptoms were

3. Corner, E. M., and Fairbank, H. A. T.: *Tr. Path. Soc. London* **56**:20, 1905.

4. Speese, J.: *Ann. Surg.* **59**:727, 1914.

5. Babes, V., and Nanu: *Berl. klin. Wchnschr.* **34**:138, 1897.

6. Bonneau, R.: *Bull. et mém. Soc. d. chirurgiens de Paris* **20**:52 (Jan.) 1928.

7. Cabot, R. C.: *New England J. Med.* **202**:684, 1930.

8. Cattell, R. B., and Woodbridge, P. D.: *S. Clin. North America* **11**:363 (April) 1931.

9. Demmin, E.: *Aerztl. Sachverst.-Ztg.* **18**:76, 1912.

10. Egtermeyer, A.: *Inaug. Dissert., Greifswald*, 1920.

11. Ghon, A., and Hintz, A.: *Beitr. z. path. Anat. u. z. allg. Path.* **45**:89, 1909.

12. Glass, E., and Alsberg, J.: *Deutsche med. Wchnschr.* **48**:1108, 1922.

13. Kathe, H.: *Virchows Arch. f. path. Anat.* **187**:265, 1907.

14. Marwedel, G.: *Beitr. z. klin. Chir. (supp. 7)* **24**:104, 1899.

15. Morpurgo, B.: *Ztschr. f. Heilk.* **16**:157, 1895.

16. Richter, M.: *Deutsche Ztschr. f. Chir.* **102**:237, 1909.

17. Rieckenberg, H.: *Inaug. Dissert., München*, 1911.

18. Steiner, R.: *Beitr. z. klin. Chir.* **22**:407, 1898.

19. Wortmann, W.: *Deutsche Ztschr. f. Chir.* **123**:103, 1913.

present; death occurred suddenly, preceded by a violent attack of vomiting and by extreme weakness and pallor. In Rieckenberg's case the tumor was an incidental finding in a man, aged 70, who died of heart failure. The symptoms most frequently found were vague abdominal pain (reported in eight), sometimes associated with tarry stools, anemia, palpitation and weakness (reported in eight) and rarely accompanied by vomiting. This is in contrast to gastric myosarcoma, in which vomiting is almost invariably present. Roentgen rays were of but little assistance in the diagnosis of gastro-intestinal myosarcoma, since the growth of such tumors in all but two instances was external to the intestine, and the occasional slight roughening of the mucosal surface was suggestive merely of ulcer. A mass was palpable in only seven cases, facilitating correct diagnoses in these instances. Babes and Nanu,⁵ in 1897, reported the first case of leiomyosarcoma of the small intestine

Relation of Incidence of Leiomyosarcoma of the Small Intestine to Age in Cases Reported in the Literature

Age	Number of Cases
1-10.....	0
11-20.....	1
21-30.....	2
31-40.....	5
41-50.....	4
51-60.....	3
61-70.....	1
71-80.....	1
Over 80.....	0
Total.....	17

which was palpable, and this was also the first case in which a tumor of this type was successfully removed. Richter¹⁶ reported the second case of successful removal of a palpable myosarcoma. Since 1875, six cases have been correctly diagnosed. In one instance the mass was thought to be an ovarian cyst. In nine cases no diagnosis was made.

The size of leiomyosarcomas of the small intestine has varied considerably. The majority reached the size of a baseball; some were the size of a walnut, some the size of a baby's head. Multiple nodules were present in only one case. A tumor of phenomenal size, weighing 7 Kg., was reported by Steiner.¹⁸ In the case reported here the tumor measured 15 by 18 by 17 cm. In some cases the mass grew on a narrow base or stalk. From the reports of the gross structure of these tumors, it appears that they are characteristically hard, coarse, nodular, rather nonvascular structures, prone to degeneration in the center and to ulceration through the mucosal surface of the small intestine. Such ulcerations were described in seven of the nineteen cases. The tumors are usually infiltrating, but are sometimes encapsulated.

Metastases have been reported in only four of the nineteen cases. In the case reported by Ghon and Hintz, there were metastases to the abdominal subcutaneous tissues, thyroid, lungs, liver, pancreas, suprarenals, kidneys, mucosa of the stomach and small intestine and to many bones. In a case reported by Marwedel in a woman, aged 43, a bulky tumor of the jejunum infiltrated the mesentery and metastasized to the regional lymph nodes, right ovary and appendix. Steiner reported the case of massive jejunal tumor in a woman, aged 57, with metastasis to the mesentery. The fourth case with metastases is the one here presented.

In general, lymphosarcoma of the small intestine resembles that of the stomach. Except for its location, the tumor found in our patient is similar to that described by Melnick.²⁰

It is likely that many leiomyosarcomas have passed unrecognized, especially before the technic of staining the protoplasmic fibrillae was developed. The literature contains discussions as to the origin of tumors of smooth muscle, their malignancy and their embryonic reversion. Certain microscopic features are, however, common to the cases reported. Most frequent mention was made of the interwoven bundles of spindle cells, usually arranged in columns and palisades, and of the pleomorphism of the nuclei. The majority of the nuclei were rod-shaped, large and hyperchromatic, but multinucleated tumor cells were mentioned in somewhat less than half of the descriptions. Mitoses were relatively rare. The stroma was usually scanty and nonvascular. With Mallory's phosphotungstic acid and Masson's trichrome stains, delicate protoplasmic fibrillae could be demonstrated.

SUMMARY

A case is reported of duodenal leiomyosarcoma with symptoms referable to repeated hemorrhage into the intestine for five years, compression of the inferior vena cava for seven weeks and a palpable tumor in the right side of the abdomen for six weeks. The tumor compressed the inferior vena cava, and thrombi were formed in both common iliac veins. Death resulted from pulmonary embolism. This case and the eighteen other cases of leiomyosarcoma of the small intestine which have been reported in the literature are analyzed.

20. Melnick, P. J.: *Am. J. Cancer* **16**:890, 1932.

PRIMARY MALIGNANT LYMPHOCYTOMA OF THE PROSTATE GLAND

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Among the rarer malignant tumors of the prostate gland are sarcoma, rhabdomyoma and lymphocytoma. Only eight reports concerning the last-mentioned type are found in the literature (table). Because of the rarity of these tumors this report of lymphocytoma of the prostate gland seems worthy of presentation.

REPORT OF CASE

A ball player and fireman, aged 41, entered the hospital complaining of pain and distress following urination for three weeks. Moderate subacute urinary cystitis of undetermined etiology was found. Examination of the blood showed 100 per cent hemoglobin and a leukocyte count of 9,900, with a normal differential count. The red cells were not counted. The bleeding time and the coagulation time were normal. Nonprotein nitrogen was 42.8 mg. per hundred cubic centimeters; urea nitrogen, 26.6 mg.; sugar, 85.1 mg., and creatinine, 1.2 mg. The Wassermann and Kahn tests were negative. Staphylococci and albumin were found in the urine.

Cystoscopic examination at this time showed obstruction of the prostatic urethra, and the passage of the cystoscope caused bleeding. The bladder was described as inflamed; the prostate, as having an enlarged right lobe. No ulcers or tumors of the bladder were present. Rectal examination disclosed a "hard nodule in the right lobe of the flat, broad prostate." Twenty-six days later an exploratory perineal section was made and the prostate was found "enlarged, firm, thickened and tending to bulge through the capsule when the latter is incised." A portion was removed and the pathologist made a diagnosis of "benign hypertrophy of the prostate with acute and subacute inflammation." The patient remained at rest in bed. Seventy-five days later the physician was unable to pass the cystoscope. Three days after this a suprapubic section revealed a large growth that projected into the bladder. The mass was friable and extended about the meatus. Bleeding was profuse on manipulation. Biopsy at this time revealed a "medullary carcinoma of the prostate." Roentgen examination of the dorsal spine, the ribs and the pelvis revealed no evidence of metastases. The time from the onset of symptoms to death was two hundred and sixty-five days.

Autopsy revealed: primary malignant tumor of the prostate with metastases to the seminal vesicles, bladder, kidneys, mesentery, suprarenal glands, pancreas and capsule of Glisson; bilateral hydro-ureter and hydronephrosis with ascending pyelonephritis on the left side and pyelitis on the right side; emphysema of the lungs; emaciation; a suprapubic cystostomy scar, and a perineal section scar.

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The tumor, with the involved pelvic viscera and the bladder, weighed 1,680 Gm. It measured 13 cm. in the anteroposterior diameter, 15 cm. in the transverse diameter and 16 cm. in the greatest superior-inferior diameter. The capsule was thin. In the subcapsular spaces were numerous diffuse arterial and venous ramifications containing dark red clotted blood. Infiltrating and surrounding the hypertrophied muscle bundles of the urinary bladder were distinct areas of grayish-white new growth. The cavity of the bladder measured 7 cm. in its lateral diameter and 5.5 cm. in its anteroposterior diameter. The base was raised by multiple,

Essential Data on Clinical and Pathologic Manifestations of Lymphatic Tumors of Prostate

Author	Age, Years	Duration	Size	Extension	Metastases	Type
Coupland ⁸	29	5 months	8 inches (20.3 cm.) in circumference 3.5 inches (8.8 cm.) in length	Bladder	Pancreas, rib and right supra-renal gland	Lymphoma
Kaufmann: Deutsches Clin. 53 : 394, 1902	24½	Not given	Slightly smaller than a fist; frontal plane, 6 by 4.5 cm.	Bladder, posterior portion of urethra and seminal vesicles	Pleura, kidneys, dura, pancreas, cervical lymphatics femur, tibia and cranial vault	Lympho-sarcoma
Conforti and Favento: Folla urol. 1 : 180, 1907-1908	45	4 months after operation	7 cm. in height; 10 cm. in width	Bladder, left ureter and urethra	Left kidney	Lympho-sarcoma
Quinby ^{7*}	41	5 months	Not given	Perineum	Brain	Lympho-blastoma
Symmers ⁵	30	3 months	9 cm. in diameter; 7 cm. in length	Bladder, seminal vesicles and psoas muscles	Retroperitoneal lymph-glands, kidneys, liver and left pleura	Lympho-sarcoma
Bumpus ^{4*}	28	8 months	Not given	Not given	Not given	Lympho-sarcoma
Bumpus ^{4*}	64	Patient living 2 years after extirpation	Not given	Bladder	Not given	Lympho-sarcoma
Zeno, Cid and Eroole: Rev. de cir. de Buenos Aires 10 : 212, 1931*	28	6½ months	Not given	Bladder and posterior portion of urethra	Liver and left inguinal lymph nodes	Lympho-sarcoma

* In these instances autopsies were not made. The diagnosis was made on the basis of biopsy.

grayish-white, smooth, glistening nodules which did not rupture the mucosa. The largest of these, to the right of the urethral orifice, measured 2.5 cm. by 1.5 cm. in its various lateral and anteroposterior diameters and extended 1.75 cm. above the floor of the bladder. The posterior portion of the urethra was markedly dilated, and the lumen was invaded by several large polypoid new growths. A midsagittal section of the tumor revealed white, glistening, somewhat rubbery, firm surfaces in which no definite prostatic tissue was observable. The cellular tissue was arranged in large and small islands separated by extremely thin strands of fibrous connective tissue. The muscularis and submucosa of the anterior wall of the rectum were infiltrated with new growth, which, however, did not penetrate the mucosa. The tumor completely invested the seminal vesicles. The small, compressed, yellowish-brown vesicular ducts were sharply demarcated from the surrounding new growth. The lumens of the ducts gave no gross evidence

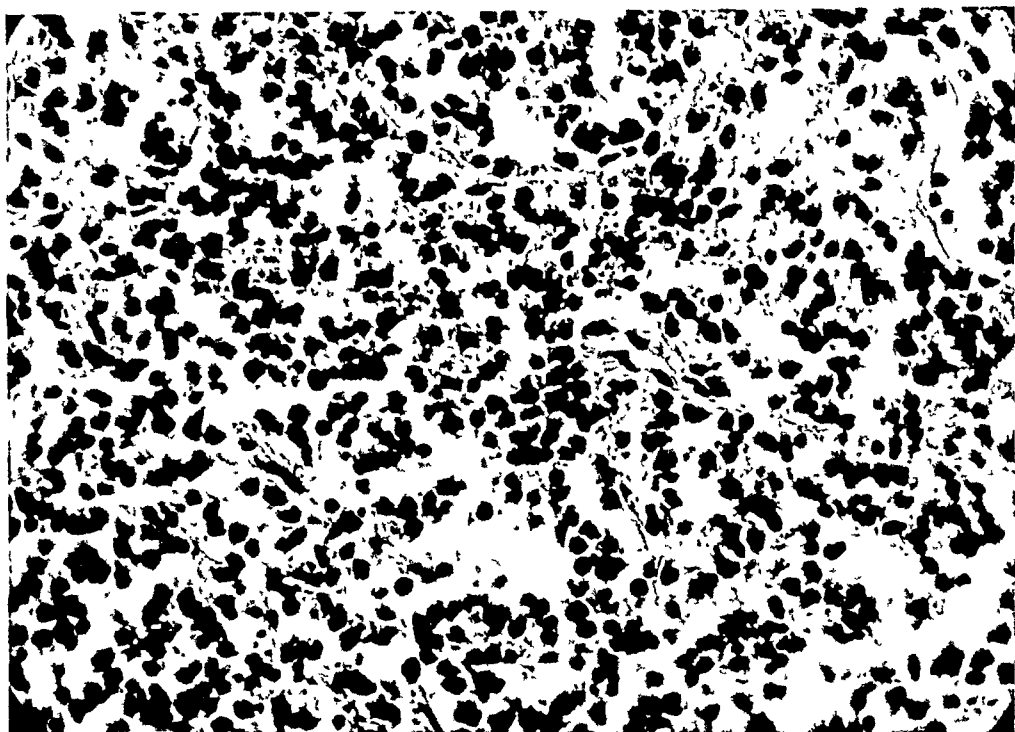


Fig. 1.—Photomicrograph revealing the character of the cells. The poor differential staining is not due to improper fixation since the biopsy specimen showed the same evidence of degeneration.

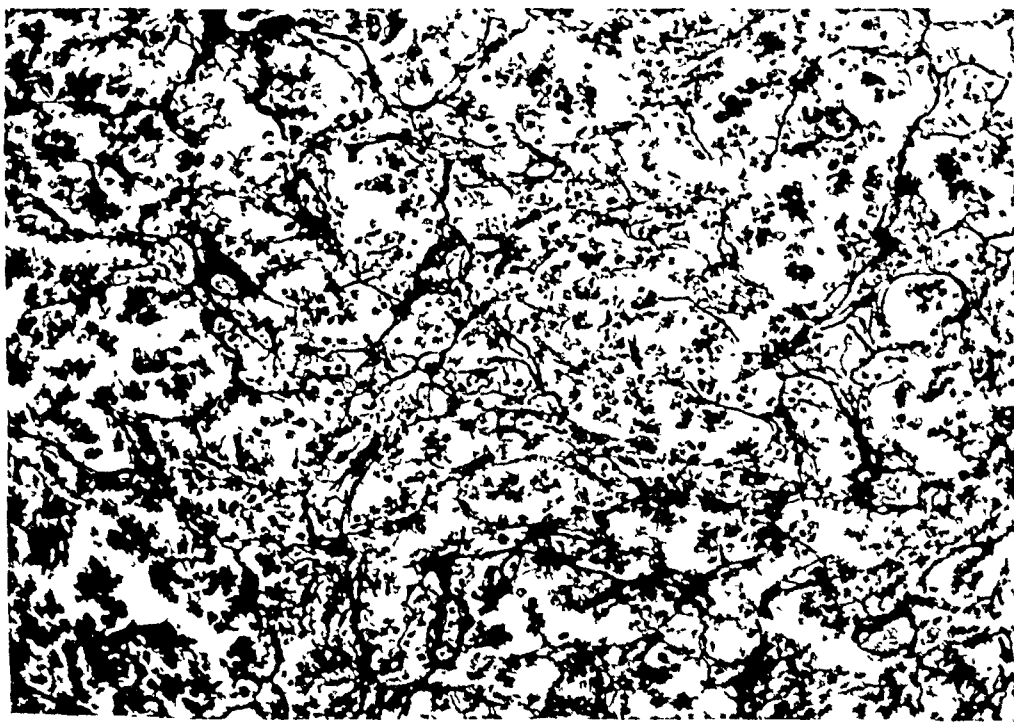


Fig. 2.—Photomicrograph of a metastatic nodule in the pancreas, illustrating the character of the reticulum (Foot's modification of Bielschowsky's stain).

of invasion by the tumor. There was no evidence of cystitis, but the renal pelves contained pus.

Microscopic examination of sections from the center of the tumor showed numerous, closely packed, small, round cells growing diffusely throughout a delicate reticular and vascular stroma (fig. 1). The nuclei were hyperchromatic and from round to oval. The cytoplasm was scant and stained faintly with the acid dyes. Mitotic figures were infrequent. The stroma as seen with special silver stains was composed of fine, threadlike, fibrillar, black strands interwoven diffusely throughout the tissue separating various-sized masses of cells. The delicate fibers anastomosed freely with the single layer of flattened cells comprising the walls of the blood vessels. Sections from the capsular portion of the tumor revealed thin, vascular fibrous connective tissue in which cross-sections of nerve fibers were present. The perineurium here was continuous with many of the small reticular fibrillae that permeated the tumor tissue. The tumor cells were similar to those in the center of the tumor. In neither region was there any observable tendency toward alveolar formation. In the metastases the stroma and cells were similar in type and arrangement to those described.

The predominance of lymphocyte-like cells with a definite reticulum, in the primary as well as in the secondary growths, together with the absence of metastases to the bone and other characteristics of carcinoma led to the conclusion that this was an instance of malignant lymphocytoma of the prostate, although the exact characteristics of the cell type were difficult to determine because of the antemortem degeneration and anaplasia.

COMMENT

The age of incidence of lymphosarcoma of the prostate extends from 24½ to 64 years, the average being approximately 32. Bumpus¹ stated that any neoplasm of the prostate gland occurring before the fortieth year of life should be considered as sarcoma, as his study of one thousand cases of carcinoma of the prostate gland revealed none before this age. Powell² pointed out that 25 per cent of the cases of sarcoma occur in persons above the age of 30. The duration of the disease was given in six of the seven reported instances of sarcoma with a fatal termination (table). The most rapidly progressing case was that of Symmers³ in which the course was only three months. The case reported by Bumpus,⁴ which occurred in a 28 year old man, extended over eight months. The average course for the six cases was approximately 5 months. The case reported here was of approximately nine months' duration from the onset of symptoms to death. Individual variations in the rapidity of the course undoubtedly occur, although Smith and Torgeson⁵ concluded that the round cell type of

1. Bumpus, H. C.: *Surg., Gynec. & Obst.* **43**:150, 1926.

2. Powell, R. E.: *Canad. M. A. J.* **18**:509, 1928.

3. Symmers, D.: *Arch. Surg.* **6**:755, 1923.

4. Bumpus, H. C.: *J. Urol.* **14**:519, 1925.

5. Smith, R., and Torgeson, W.: *Surg., Gynec. & Obst.* **43**:328, 1926.

sarcoma is more malignant than lymphosarcoma. On the basis of the cell type one would anticipate the reverse. The conflict of opinion may be due to inaccuracy of terminology.

In the four cases in which necropsy was performed the prostatic growths varied from 4.5 cm. to 8.9 cm. in height and from 6 to 10 cm. in width, the average height and width being 6.8 and 8.2 cm., respectively. The tumor in the case reported here was large (13 by 15 by 16 cm.). The consistency of a lymphosarcoma of the prostate may be soft and boggy or hard and tense.

The urinary bladder is the most common site of extension; it was involved in six of the eight cases reported. The posterior portion of the urethra was invaded in three instances, and the seminal vesicles were implicated in two. There was definite evidence of invasion of the blood stream in three cases. The para-aortic lymphatics were involved in two of the four cases in which autopsy was performed. In the case recorded here the marked infiltrative growth into the bladder and about the seminal vesicles, as well as the limitation of the metastases to the abdomen, without involvement of the liver or the osseous system, speaks for lymphatic dissemination, although there was no observable implication of the para-aortic chain. Although, as MacCallum⁶ observed, lymphosarcoma tends to spread regionally, it is extremely difficult at times to eliminate the possibility of hematogenic dissemination.

With the exception of the case reported by Quinby⁷ in which the predominating cell resembled the lymphoblast, none of the other instances of lymphosarcoma of the prostate gland were differentiated as to cell type. In the two cases recorded by Bumpus, descriptions of the predominating cell type were not included. The remaining five cases, including Coupland's,⁸ undoubtedly fall into the group of malignant lymphocytoma. The size of the cell is the main point of distinction. In the instance reported here the predominating cell closely resembled the small lymphocyte in size, shape and structure.

The occurrence of primary lymphosarcoma of the prostate was challenged by Ewing⁹ on the basis that this gland does not normally contain adenoid tissue and that the so-called lymphosarcoma in reality is nothing more than extremely anaplastic small cell carcinoma. Symmers³ stated that the prostate belongs to the so-called auxiliary lymphatic system in that it contains interstitial lymphoid foci, which, though often over-

6. MacCallum, W. G.: *Textbook of Pathology*, ed. 5, Philadelphia, W. B. Saunders Company, 1932.

7. Quinby, W. C.: *J. Urol.* **4**:137, 1920.

8. Coupland, Sidney: *Tr. Path. Soc. London* **28**:179, 1877.

9. Ewing, James: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

looked, are readily seen in certain conditions. The infrequency of this type of tumor, he explained, is due to the fact that the lymphoid cell rests are numerically insignificant and functionally dormant and undergo hyperplasia only under unusual circumstances. Whether the disturbance in cellular equilibrium is created by bacteria, by their toxins, or by by-products of necrosis is difficult to say. However, in seven of the eight cases of lymphosarcoma of the prostate gland reported in which an adequate abstract of the clinical history was included, there was a history of a preexisting prostatitis in four. This inflammatory condition serving as a continuous source of irritation is accepted as the most probable etiologic factor in epithelial tumors of this organ. There is no reason to suppose that its effect may not occasionally manifest itself on the less frequent, less abundant lymphoid foci as it commonly does on the more numerous, highly functional epithelial cells. That lymphosarcoma may well be primary in this organ seems more certain when one considers that lymphoma of lymphatic leukemia may be found in the prostate (Karsner¹⁰).

CONCLUSIONS

Lymphosarcoma of the prostate, although rare, should be considered in the differential diagnosis of prostatic tumors.

Lymphosarcoma in this organ probably arises from small, nonfunctional, interstitial lymphoid foci.

Tumors of the type reported usually are large, rapidly growing and of varying consistency, but their histologic structure is relatively constant.

Although lymphosarcoma tends to spread regionally, hematogenic dissemination must be considered.

Malignant lymphocytoma of the prostate gland is more common than large round cell lymphosarcoma or lymphoblastoma.

10. Karsner, Howard T.: *Human Pathology*, ed. 3, Philadelphia, J. B. Lippincott Company, 1931.

AVITAMINOSIS

XVI. PRODUCTION OF GASTRIC ULCERS IN THE ALBINO RAT AS A RESULT OF SPECIFIC INFLUENCE OF DEFICIENCY OF VITAMIN B

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In a previous publication Sure, Thatcher and Walker¹ reported that in weaned albino rats deprived of the vitamin B complex the pathologic changes were mainly those associated with inanition. In addition, hypertrophy of the suprarenal glands and of the heart had been observed. In weaned animals suffering from uncomplicated deficiency of vitamin B atrophy of the spleen and hypertrophy of the suprarenal glands and heart were also noted, but the significance of the latter observations was attached to the fact that such changes occurred in animals that were in states apparently uncomplicated by inanition. The dietary regimen, however, was not clearcut for the differentiation between pathologic changes produced by the specific influence of vitamin B and by under-nutrition because of insufficient intake of food.

METHODS

In this investigation the dietary technic that was previously described² was employed; briefly stated, it consisted in the daily restriction of rats of the same sex, weighing from 40 to 100 Gm., to the same volume of water and amount of food consumed by their litter-mates, which received the diet deficient only in vitamin B or the vitamin B complex; however, in addition, the animals on the restricted diets were allowed vitamin B, either dried baker's yeast incorporated in the ration or a vitamin B concentrate (prepared by one of us, B. S.), separately from the diet. As the plane of nutrition was controlled, the difference in growth and the accompanying pathologic changes produced must be attributed to the specific influence of the B vitamin or the B vitamins, depending on whether vitamin G was furnished in the ration. Thirteen such pairs of experiments were

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1. Sure, Barnett; Thatcher, H. S., and Walker, D. J.: Arch. Path. **11**:413, 1931.

2. Sure, Barnett; Kik, M. C., and Smith, M. E.: J. Nutrition **5**:155, 1932.

employed for the study of the specific influence of the vitamin B complex and eleven pairs for the specific effect of vitamin B on the histologic changes in various tissues.

Four mothers and litters on diets deficient only in vitamin B were also studied, in triads, as follows: Lactating rats were transferred on the day of the birth of their litters, reduced to six, from stock diet 1³ to ration 1865, which is satisfactory in every respect with the exception of vitamin B content. It is of this composition: casein (purified), 20; salt mixture 185,⁴ 4; autoclaved yeast, 10; butter fat, 10, and dextrin, 56. Litter-mates were restricted to the same amount of water and food of the same diet, but the yeast contained in the ration was untreated. The only limiting factor in such a dietary regimen, since the plane of nutrition was controlled, was vitamin B, which was destroyed during the process of autoclaving. Another group of litter-mates was fed the same ration containing 10 per cent of the untreated yeast, but the daily intake of food and water was unrestricted. The difference between the second and third groups must be due to inanition, since the only limiting factor was the plane of nutrition.

In addition, three groups of experiments were studied in quadruplicate so as to determine not only the influence of restricted food but also that of restricted water consumed by the avitaminotic rats.

After the completion of the experiments, the tissues were fixed immediately in formaldehyde. They were stained with hematoxylin and eosin. Practically all of the principal tissues of seventy animals were studied in entirety. These tissues included the heart, lungs, liver, spleen, kidneys, genitalia, suprarenal glands, salivary glands, tongue, pancreas, stomach and intestines. As few changes were found in the seventy animals in addition to those previously reported,¹ fewer tissues were examined in the remainder of the sixty-one animals; in these, observations were made on the heart, lungs, kidneys, spleen, liver and testes.

Records were kept of the body weights of all the animals and of the weights of the liver, spleen, heart, kidneys and suprarenal glands in several groups of animals suffering from deficiency of the vitamin B complex and in several groups of rats suffering from uncomplicated deficiency of vitamin B. These results are given in tables 1 and 2.

RESULTS

The results corroborate the previous findings of Sure and his co-workers⁵ that vitamin B not only produces growth by stimulating the appetite, but exerts a specific influence on growth unrelated to the plane of nutrition, in the same sense as certain amino-acids and certain mineral elements exert their influence on growth. As an example of the uncomplicated deficiency of vitamin B, rat 12 ♂ lost 14 Gm. during the experimental period of sixty-three days, and its litter-mate, which was restricted to the same daily amount of food and volume of water, gained 26 Gm. during the same period. Similarly, rat 5 ♂ maintained its weight only during the experimental period of fifty-seven days, while its litter-mate, rat 15 ♂, gained 76 Gm. while on the same daily plane of nutrition.

3. Sure, Barnett: *J. Biol. Chem.* **69**:65, 1926.

4. McCollum, E. V., and Simmonds, N.: *J. Biol. Chem.* **33**:63, 1918.

5. Sure, Barnett: *J. Biol. Chem.* **97**:133, 1932. Sure, Kik and Smith.²

TABLE 1.—*Specific Effect of a Deficiency of the Vitamin B Complex on the Weight of the Body, Suprarenal Glands and Organs of the Albino Rat*

P* Ani- mal	R* Ani- mal	Experi- mental Period, Days	Body Weight		Weights of Organs and Percentage of Total Body Weight									
			Begin- ning of Experi- ment, Gm.	End of Experi- ment, Gm.	Liver		Spleen		Heart		Kidney		Suprarenal Glands	
					Weight, Gm.	Per Cent	Weight, Gm.	Per Cent	Weight, Gm.	Per Cent	Weight, Gm.	Per Cent	Weight, Gm.	Per Cent
6 ♀	7 ♀	41	51	43	0.0550	0.20	0.2598	0.40	0.8098	2.07	0.0089	0.019
		41	53	79	0.1730	0.22	0.5132	0.60	0.8566	1.98	0.0210	0.026
8 ♀	9 ♀	68	52	57	2.3119	1.24	0.1872	0.31	0.2180	0.43	0.8950	1.57	0.0130	0.025
		68	55	105	5.5390	5.27	0.2230	0.21	0.1818	0.46	1.7680	1.69	0.0183	0.017
10 ♀	11 ♀	73	70	55	3.0185	5.18	0.2081	0.38	0.3910	0.71	1.0064	1.82	0.0223	0.041
		73	52	117	4.0962	1.27	0.3722	0.31	0.4949	0.42	1.2000	1.08	0.0352	0.030

* P indicates pathologic; R, restricted to the same plane of nutrition; ♀, female.

TABLE 2.—*Specific Effect of Uncomplicated Deficiency of Vitamin B on the Weight of the Body, Suprarenal Glands and Organs of the Albino Rat*

P* Ani- mal	R* Ani- mal	Experi- mental Period, Days	Body Weight		Weights of Organs and Percentage of Total Body Weight									
			Begin- ning of Experi- ment, Gm.	End of Experi- ment, Gm.	Liver		Spleen		Heart		Kidney		Suprarenal Glands	
					Weight, Gm.	Per Cent	Weight, Gm.	Per Cent	Weight, Gm.	Per Cent	Weight, Gm.	Per Cent	Weight, Gm.	Per Cent
12 ♂	13 ♂	63	62	48	1.7610	3.67	0.0600	0.19	0.2176	0.51	0.9100	1.90	0.0150	0.031
		63	81	110	1.8551	1.11	0.3230	0.30	0.4772	0.43	1.2000	1.69	0.0196	0.018
4 ♂	11 ♂	53	81	60	1.9103	3.23	0.0831	0.14	0.3000	0.50	0.9610	1.50	0.0236	0.029
		53	97	114	3.7832	3.32	0.4067	0.36	0.4612	0.46	1.1410	1.00	0.0090	0.008
5 ♂	15 ♂	57	55	55	2.7811	5.05	0.1180	0.27	0.2598	0.47	0.9035	1.64	0.0137	0.025
		57	56	126	5.0200	1.07	0.3200	0.26	0.5000	0.39	1.3400	1.06	0.0166	0.013
6 ♂	17 ♂	59	47	37 D	1.6524	1.57	0.0800	0.22	0.1872	0.50	0.8570	2.31	0.0118	0.040
		59	47	70	3.5200	5.03	0.2550	0.36	0.2970	0.42	1.1312	1.62	0.0231	0.033

* P indicates pathologic; R, restricted to the same plane of nutrition; D, died; ♂, male.

The results of the growth of the animals fed the vitamin B complex are comparable to those cited for the animals fed vitamin B.

The weights of the organs are expressed as percentage of the total body weight. It is apparent that hypertrophy of the suprarenal glands is not the result of inanition, but is due to the specific influence of the deficiency of vitamins, since the weight of the suprarenal glands, as percentage of body weight, is much greater in the pathologic animals than in the restricted controls. In the group fed the vitamin B complex, two of three sets showed hypertrophy of the suprarenal glands due to the specific influence of the vitamin. In this connection, it may be pointed out that the injury produced in animals deprived of all the B vitamins is frequently so severe that the animals die before the investigator has an opportunity to search for and find pronounced chemical or histologic changes. For this reason, it often is advantageous to produce partial instead of complete deficiency of avitaminosis in experimental animals. Animals receiving diets deficient only in vitamin B live for longer periods and in them one often finds considerably more damage, as evidenced by microscopic studies. This was true in the case of our finding of gastric ulcers, as will be brought out later.

An additional point, as is evidenced from an analysis of the weights of the organs, is that a deficiency of vitamin B *per se* produces hypertrophy of the kidneys.

No specific influence of deficiency of vitamin B is apparent on the weights of the liver and the heart.

Although the histologic analyses indicated atrophy of the spleen in the animals on a restricted diet as well as in the pathologic animals, three of the five groups (as judged by the weights of the organs expressed as percentage of body weight) showed atrophy produced by a deficiency of vitamin B *per se*.

The animals fed diets deficient in vitamin B and the vitamin B complex, compared with the controls on a restricted diet, showed immaturity of the testes.

Perhaps our most significant result in the investigation is the finding of gastric ulcers as a result of the specific influence of a deficiency of vitamin B.

GASTRIC ULCERS

In 1931 Sure, Thatcher and Walker¹ reported a gastric ulcer in the stomach of a weaned rat suffering from uncomplicated deficiency of vitamin B. Another ulcer was discovered in a recut from some of this material after the article had been published. Ulcers of the stomach were also observed in several polyneuritic, nursing young of the albino

rat.¹ Thatcher, Sure and Walker also reported⁶ an ulcer in the rumen of the stomach of a rat suffering from deficiency of vitamin G and a small abscess in the stomach of another rat caused by the same deficiency. However, serial sections were not made because of the extensive technical requirements, and because at that time we were studying many other organs. In the meantime, Dalldorf and Kellogg⁷ reported (1932) gastric ulcers in albino rats fed diets deficient in vitamin B. They found 73 per cent of a group with seventy-four observed lesions. Eight of these were chronic, indurated ulcers resembling peptic ulcers in man. It is not apparent, however, from the character of the results of the latter investigators whether the gastric ulcers were produced as a result of inanition or of a deficiency of vitamin B per se. As our control rats were restricted daily to the same plane of nutrition as our pathologic animals, the complication of inanition has been circumvented in our investigation.

Besides the ulcers reported, our experimental work with serial sections of stomachs included those of four rats fed a diet deficient in the vitamin B complex, those of four rats fed a diet deficient in vitamin B and those of eight controls. The entire stomach was mounted, so that the location of the lesion could be obtained. The sections averaged from about 6 to 7 microns in thickness, but those from the controls were from about 15 to 20 microns thick. Every third section was mounted in the stomachs of the animals fed a deficient diet, and all of the sections of the controls were examined. They were stained with hematoxylin and eosin. About 16,000 sections were studied. The animals suffering from a deficiency of the B complex contained no ulcers in the stomach. One of them, however, contained a large cyst between the rumen and the glandular portion in the lesser curvature. The cyst was lined with flattened epithelium, and it was surrounded by a few polymorphonuclear leukocytes.

Serial sections of 4 cm. of duodena from ten rats were studied. These duodena included three from rats on a diet deficient in vitamin B and three from rats on a diet deficient in the vitamin B complex. There were four duodena from control animals. Thousands of sections were examined microscopically, and no duodenal ulcers were found.

A description of the ulcers in the animals fed a diet deficient in vitamin B, including the two in our earlier work, is as follows:

RAT 1 ♂.—An acute ulcer had eroded the glandular portion, but did not involve the muscularis mucosae. The ulcer contained eosinophilic and neutrophilic polymorphonuclear leukocytes, many of which were undergoing degeneration; the

6. Thatcher, H. S.; Sure, Barnett, and Walker, D. J.: *Arch. Path.* **11**:425, 1931.

7. Dalldorf, G., and Kellogg, M.: *J. Exper. Med.* **56**:391, 1932.

squamous epithelium was also undergoing degeneration. Fibrin was present. The muscularis mucosa contained a few polymorphonuclear leukocytes, mainly neutrophilic, but occasionally eosinophilic with marked congestion and edema. The same changes were noted in the muscularis. A few small lymphocytes were also present. Near the tip of the ulcer there were keratin flakes and epithelial cells. A small line of dilated vessels and a few polymorphonuclear leukocytes extended into the submucosa (fig. 1).

RAT 2 ♂.—The ulcer was similar to that studied in the stomach of rat 1 ♂, except that it was deeper and there was more cellular debris. It was in the

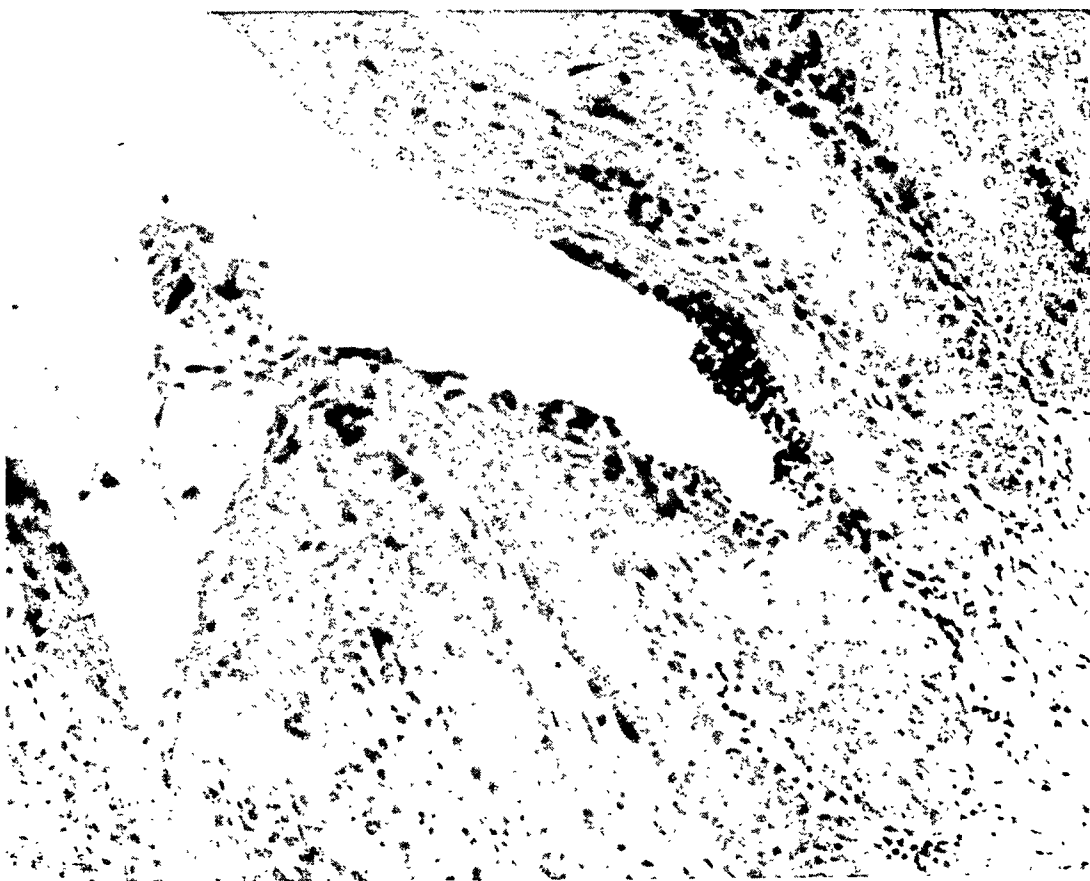


Fig. 1 (rat 1 ♂).—Photomicrograph of an acute ulcer in the glandular portion of the stomach.

glandular portion and extended into the muscularis. The debris consisted of degenerated glandular elements, eosinophilic and neutrophilic polymorphonuclear leukocytes and fibrin. Connective tissue, edema and polymorphonuclear leukocytes were at the base of the ulcer.

The following descriptions are of the ulcers in our later work, containing the serial sections:

RAT 3 ♂.—There was an acute ulcer of the glandular portion in the lesser curvature. It was small and contained polymorphonuclear leukocytes undergoing degeneration; at the base there was a slight amount of fibrin and edema. The

glandular elements were swollen and adherent. At the edges the nuclei were pyknotic. Another smaller ulcer was in the greater curvature at the tip of the glandular portion, but it consisted only of an erosion containing cellular debris and polymorphonuclear leukocytes undergoing degeneration. The third ulcer, which was chronic, extended into the muscularis, even to the outer layer. It was in the lesser curvature and closer to the esophagus than the others. The base consisted of fibroblasts, small lymphocytes and a few eosinophilic polymorphonuclear leukocytes. This portion was edematous. The crater, which was at the lower edge where the rumen should be, consisted of degenerating polymorphonu-



Fig. 2 (rat 3 ♂).—Chronic ulcer in the rumen of the stomach. (Photograph of a drawing.)

clear leukocytes and epithelial cells, as well as fibrin and keratin flakes. New and dilated blood vessels were at the base (fig. 2).

RAT 4 ♂.—The ulcer extended about two thirds of the distance into the squamous epithelium. Red blood cells undergoing degeneration were present, as well as keratin flakes and epithelial cells in the process of degeneration. The ulcer was divided by a region of keratinized epithelium, and the same type of epithelium extended far out over the edge. It was acute and in the rumen at the juncture of the glandular portion about the same distance from the pylorus as from the esophagus. It was in the lesser curvature.

RAT 5 ♂.—A small erosion was present in the glandular portion, extending almost to the muscularis mucosa. It contained remnants of glandular elements, cellular débris and polymorphonuclear leukocytes. It was in the lesser curvature near the pylorus.

Although only five lesions were found in eight rats, the majority occurred in the region of the stomach where they are usually found in man. These microscopic lesions represent acute and one chronic ulcer such as are present in many. The rats with ulcers included in our series were those which were suffering from a deficiency in vitamin B and not from a deficiency of the two vitamins (B and G).

Stimulated by the early work of McCarrison⁸ on the production of gastric ulcers in dietary deficiencies, Seale Harris⁹ has reported marked success in the cure of gastric and duodenal ulcers with diets abundant in vitamins. It is now apparent from the character of our results and from the recent findings of Dalldorf and Kellogg⁷ that a deficiency of vitamin B is one of the causes for the production of gastric ulcers experimentally.¹⁰ Our results, therefore, may be of interest to the gastro-enterologist. Since the diets of patients suffering from chronic peptic ulcers have to be restricted to certain foods that are nonirritating to the gastric mucosa, it is not always possible to select a dietary regimen that will furnish optimum amounts of vitamin B. In such cases it is suggested to experiment clinically with a concentrated vitamin B extract as a supplement to the daily diet.¹¹

SUMMARY

Gastric ulcers have been produced in the albino rat as a result of specific deficiency in vitamin B, uncomplicated by the factor of inanition. It is suggested that vitamin B therapy may be indicated in human gastric ulcer.

8. McCarrison, Robert: *Studies in Deficiency Diseases*, London, Henry Frowde, Hodder & Stoughton, 1921.

9. Harris, Seale: *J. A. M. A.* **91**:1452, 1928.

10. That gastric, pyloric and duodenal ulcers may be produced in the guinea-pig by a deficiency of vitamin C has been recently reported by Smith and McConkey (*Arch. Int. Med.* **51**:413, 1933).

11. Sure, Barnett: *The Vitamins in Health and Disease*, Baltimore, Williams & Wilkins Company, 1933.

LATENT PORTAL CIRRHOSIS OF THE LIVER

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MINNEAPOLIS

In the literature one finds occasional reference to the accidental finding post mortem of cirrhosis of the liver in persons who had presented no clinical evidence of this disease.

Fagge¹ wrote in 1875: "At the hospital the liver was accidentally found to be cirrhotic in persons who had died of injury or of some other disease once for every two cases in which it had been the cause of death. In many of these cases the organ was indurated in an extreme degree; yet it is certain that the patients suffered from none of the more marked symptoms of such an affection." This conclusion was drawn from the consideration of 130 patients with cirrhosis, and of this number he apparently believed that 58 died of causes other than cirrhosis. Yeld,² in 1898, reported 126 cases of alcoholic cirrhosis and found that in 59, or 46.8 per cent, the condition was latent. Candler³ reported 85 cases from Charing Cross Hospital and 23 from Claybury Asylum. He found that in the former group 12 patients had died as the result of accidents on the street and 10 had died of some inter-current disease, while in the latter group death was attributed to cirrhosis in but 1 case and none of the 23 patients had ascites. Rolleston^{4a} stated:

Cirrhosis of the liver is not uncommonly latent and does not give rise to any symptoms. It may be found in the bodies of persons who have died as the result of accidents or other diseases. . . . It would be incorrect to say that when a patient dies from some other disease the cirrhosis has necessarily been entirely latent, since patients with cirrhosis rapidly die with pulmonary tuberculosis and are very bad subjects for pneumonia, erysipelas, and other acute infections. The fact, however, that out of 167 consecutive necropsies at St. George's Hospital in which the liver was cirrhotic, 86, or just over half, died from other diseases and not directly from cirrhosis, shows how frequently cirrhosis remains latent.

It appears from the foregoing findings that from 35 to 50 per cent of all cases of cirrhosis are "accidentally" found post mortem. This

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1. Fagge, C. H.: *Guy's Hosp. Rep.* **20**:155, 1875.

2. Yeld, R. A.: *St. Barth. Hosp. Rep.* **34**:215, 1898.

3. Candler, J. P., in Mott, F. W.: *Arch. Neurol. Path. Lab., London County Asylums* **3**:439, 1907.

4. (a) Rolleston, H. D., and McNee, J. W.: *Diseases of the Liver, Gall-Bladder and Bile-Ducts*, ed. 3, New York, The Macmillan Company, 1929, p. 256; (b) *ibid.*, pp. 209 and 256; (c) *ibid.*, pp. 229 and 230; (d) *ibid.*, p. 229.

is a considerable number. One wonders whether it is correct and also whether Rolleston and McNee's statement in the third sentence in the paragraph quoted goes far enough or too far. May it not be that errors are frequently made in the gross diagnosis of cirrhosis? A liver may be called cirrhotic when no cirrhosis is present. For instance, most livers which show fatty metamorphosis are rather friable, but occasionally one is quite firm and cuts with some difficulty and yet is not cirrhotic. In some cases of decompensated heart disease the consistence of the liver seems to be increased, but microscopic examination may nevertheless show no evidence of an increase of the portal connective tissue. Yeld's findings are open to criticism, since no microscopic examinations were made.

Perhaps the incidence of latent cirrhosis would not be so high if in every case all desirable information were at hand, but frequently such data are lacking. Many of the cases in the series reported in this article as latent might have to be shifted into the frankly active group if all the facts were known. It is possible that in many of them there were some symptoms of hepatic disease. The prolonged insidious onset before the appearance of unmistakable signs and symptoms in some cases of cirrhosis is well known. If all the facts were known, perhaps many of these cases should be called compensated, in the sense in which Rowntree⁵ used this term, instead of latent.

In 1902, Billings⁶ reported 54 cases of what he considered, from a clinical standpoint, to be early cirrhosis. The patients had vague gastro-intestinal symptoms, pains in the muscles, tender, firm, palpable livers and other symptoms. Ascites subsequently developed in 2. Many of them were relieved of their symptoms following the correction of dietary errors and abuses, with reduction in the size of the liver and disappearance of tenderness. That Billings was dealing with cases of early or potential cirrhosis cannot be determined; he did not represent the cases as proved but rather as suggestive.

There is marked variation in the incidence of cirrhosis in different parts of the world. Yeld,² for instance, found 164 cases in 4,117 necropsies; Candler³ found 85 in 1,099 postmortem examinations at Charing Cross Hospital and 23 in 1,271 postmortem examinations at the Claybury Asylum. Blumenau,⁷ in 12,761 necropsies, found 126 cases in which a macroscopic diagnosis of cirrhosis was made and 64 additional cases in which the diagnosis was made microscopically.

5. Chapman, C. B.; Snell, A. M., and Rowntree, L. G.: *J. A. M. A.* **97**:237, 1931.

6. Billings, F.: *Tr. A. Am. Physicians* **17**:611, 1902.

7. Blumenau, E.: *Arch. f. Verdauungskr.* **27**:1, 1920.

Rössle⁸ collected statistics published in different parts of the world, which show an incidence varying from 0.85 to 5.5 per cent. In this laboratory there were 245 microscopically proved cases of portal cirrhosis in 11,912 necropsies performed on adults, or an incidence of 2.05 per cent. The type of material available in different laboratories, even in those which are closely related geographically, doubtless varies tremendously. The material studied in this laboratory came from three large charity hospitals, a large number of private hospitals in Minneapolis and St. Paul, the coroner's service and the private practice of physicians.

All the cases recorded during the period from 1910 to 1931, inclusive, in which a gross diagnosis of cirrhosis was made post mortem and in which material was available for microscopic examination, have been studied. In some instances only a single section was preserved; in others, blocks of tissue, and in still others, the liver. An effort was made to obtain, so far as possible, sections from representative areas of each liver.

Some of these cases have been excluded because on microscopic examination there did not appear to be sufficient evidence of proliferation of connective tissue or of the bile ducts to substantiate the gross diagnosis. In this article all cases which occurred in patients under 20 years of age and all cases of pure hepar lobatum, obstructive biliary cirrhosis and definitely acute yellow atrophy were excluded.

Sections from the 245 livers were carefully studied and were divided into three groups according to the degree of cirrhotic change present. The determination of the degree of cirrhosis in each case was made independently of all clinical and postmortem information; i. e., it was based on what the sections alone showed. In many instances it was necessary to be rather arbitrary in deciding to which of the three groups a given liver should be assigned. The series showed a gradual transition from the slightest changes compatible with a diagnosis of cirrhosis to the most extreme fibrosis and distortion of the hepatic structure. In some livers different degrees of the process were found in different sections. Photomicrographs *A*, *B* and *C* (fig. 1) are type specimens illustrating the three degrees.

Sears and Lord⁹ made a somewhat similar division into four classes of a series of 78 cirrhotic livers, and placed 4 in class 1, 16 in class 2, 35 in class 3 and 23 in class 4. Only 8 of their cases were classed as latent cirrhosis.

8. Rössle, R., in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1930, vol. 5, pt. 1, p. 284.

9. Sears, G. G., and Lord, F. T.: *Boston M. & S. J.* **147**:285, 1902.



Fig. 1.—Photomicrographs showing degrees of cirrhosis; $\times 145$.

In this study the diagnosis of cirrhosis was established by microscopic examination of the liver, and the cases were then separated into active and latent groups on the basis of the clinical data and post-mortem observations. Microscopic changes in the liver were not considered in separating the active and latent cases. All cases were considered active in which there was any clinical evidence of the disease, such as gastric hemorrhage, jaundice, ascites, varices or gastro-intestinal disturbances. Cases were also considered active if postmortem examination revealed jaundice, ascites or esophageal varices, even though hepatic disease was not suspected clinically. Since the clinical history was often incomplete, it is probable that some of the cases which were classified as latent really belong to the active group. In the presence of definite cardiac decompensation, ascites was considered to be of cardiac origin. In several instances an associated disease, such as carcinoma of the stomach, made it difficult to decide whether the symptoms were of hepatic origin.

DISTRIBUTION OF CASES

As a result of this analysis, 158 of the 245 cases were classified as active and 87 as latent; i. e., 64.4 per cent were active and 35.5 per cent latent. These percentages agree with those of Fagge.¹

In the latent group, 76 of the patients were males and 11 were females, a ratio of 6.9:1. In the active group there were 110 males and 48 females, or a ratio of 2.2:1. Considering the 245 cases as a whole, there were 186 males and 59 females, or a ratio of 3.1:1.

Fagge stated: "The proportion of males to females appears from the records at the hospital to be 102 to 26, or very nearly as 4 to 1." Price¹⁰ found that of his group of 142 patients 26 per cent were females, a ratio of approximately 3:1. In Yeld's² group there were 102 males and 29 females. This is almost identical with the ratio in Fagge's group. In Candler's³ group there were 91 males and 27 females, a ratio of 3.3:1. Rolleston and McNee¹¹ gave the ratio as "about 3 to 1." Their ratio was apparently arrived at from collected statistics, including those cited here.

However, the ratio of males to females in this series needs to be corrected. In the postmortem service of this laboratory the ratio of males to females between the ages of 20 and 89 years is almost exactly 2:1 (10,920 necropsies; 7,293 males, 3,627 females). When this fact is considered it is found that for the latent group the ratio becomes 3.5:1, for the active group, 1.1:1 and for the whole series, 1.5:1. This indicates only a moderate preponderance of males and bears out the statements of Yeld² and of Rolleston¹¹ that cirrhosis is latent more often in males.

10. Price, J. A. P.: *Guy's Hosp. Rep.* **27**:295, 1884.

Fagge¹ found that the average age of the patient with latent cirrhosis at the time of death was about five years greater than that of the patients who died of active cirrhosis. According to Yeld, the average age in the latent group (56 patients) was 48.9 years and in the active group (56 patients) 46.5 years. Sears and Lord⁹ found that the patients with latent cirrhosis were about two years older than those with active cirrhosis. Fagge also found that the greatest number of patients with active cirrhosis died between the ages of 40 and 50 years. In the series described in this article the average age in the latent group was 55.8 years, and in the active group, 54.3 years. However, to state an average age for this group is misleading, since only adults were considered. The distribution according to decades gives a clearer conception of the time of life when patients with cirrhosis of the liver are seen.

TABLE 1.—*Distribution of Cirrhosis According to Age and Sex*

Age, Years	Latent Cases			Active Cases		
	Males	Females	Per Cent	Males	Females	Per Cent
20-29.....	5	0	6.0	2	2	2.7
30-39.....	5	0	6.0	12	7	12.8
40-49.....	12	2	17.0	16	9	16.8
50-59.....	20	3	28.0	33	11	29.7
60-69.....	18	3	25.6	22	11	22.2
70-79.....	9	1	12.1	16	6	14.8
80-89.....	3	1	4.8	0	1	1.4
Adults, age unknown.....	4	1		9	1	
Total.....	76	11		110	48	

It may be noted from table 1 that the maximum incidence of both latent and active cirrhosis is in the sixth and seventh decades. Practically 70 per cent of both groups of patients were between the age of 40 and 69 years. The incidence in the third and fourth decades is approximately the same as in the eighth and ninth. The difference in age in the two groups is practically negligible. It is worthy of mention that of 5 cases of cirrhosis in persons over 80 years of age, only 1 was the active type.

The simple numerical distribution of this series of cases, according to sex, age, degree of microscopic change and the presence or absence of symptoms indicates a great variation in the frequency of the process in corresponding decades. This variation is probably the result of the large error introduced by subdivision into so many small groups. By using percentages instead of actual numbers and by eliminating sex, a different impression is obtained. This distribution has been made in two ways: first, by considering the latent and active groups separately (table 2) and, second, by considering the series as a whole (table 3).

From a study of table 2, it is evident that in both the latent and the active type the greatest incidence is in the sixth decade, 27.9 per cent

of the latent cases and 29.5 per cent of the active group being found here. It is also to be noted that in the latent group the highest percentage is in grade 1 cirrhosis, whereas in the active type the highest percentage is in grade 3 cirrhosis, and that in each instance this is in the sixth decade. There is no evidence that the more advanced degrees of cirrhosis were more frequent in the older patients. It does not appear

TABLE 2.—*Percentage Distribution of Latent and Active Cirrhosis of Each Type According to Age and to Degree of Microscopic Change*

	Latent Cases				Active Cases			
	Degree of Change			Total Number	Degree of Change			Total Number
	1	2	3		1	2	3	
Number of cases.....	35	28	19	82	23	32	93	148
Age, Years								
20-29.....	2.4	1.2	2.4		1.3	0.0	1.3	
30-39.....	1.2	3.6	1.2		0.6	3.3	8.7	
40-49.....	4.8	3.6	8.5		2.7	1.3	12.8	
50-59.....	12.2	10.9	4.8		3.3	6.7	19.5	
60-69.....	9.6	10.9	4.8		3.3	4.7	14.8	
70-79.....	10.9	1.2	0.0		4.0	4.7	5.4	
80-89.....	1.2	2.4	1.2		0.0	0.6	0.0	
Per cent.....	42.3	33.8	22.9	99.0	15.2	21.3	62.5	99.0
Adults of unknown age.....	2	1	2		2	2	6	

TABLE 3.—*Percentage Distribution of Both Types of Cirrhosis According to Age and to Degree of Microscopic Change*

	Degree of Change						Total Number
	1		2		3		
	Latent Type	Active Type	Latent Type	Active Type	Latent Type	Active Type	
Number of cases.....	35	28	19	23	32	93	230
Age, Years							
20-29.....	0.8	0.8	0.4	0.0	0.8	0.8	3.6
30-39.....	0.4	0.4	1.3	2.1	0.4	5.6	10.2
40-49.....	1.7	1.7	1.3	0.8	3.0	8.2	16.7
50-59.....	4.3	2.1	3.9	4.3	1.7	12.6	28.9
60-69.....	3.4	2.1	3.9	3.0	1.7	9.5	23.6
70-79.....	3.9	2.6	0.4	3.0	0.0	3.4	13.3
80-89.....	0.4	0.0	0.8	0.4	0.4	0.0	2.0
Total per cent.....	14.9	9.7	12.0	13.6	8.0	40.1	98.3

from this table that if the persons with latent cirrhosis had lived long enough, active cirrhosis would have developed eventually. The totals, both numerically and from the standpoint of percentages, in each degree of latent cirrhosis show a progressive decrease as one passes from the least advanced to the most advanced process. The converse is true of active cirrhosis; i. e., there is a progressive increase in the totals in each degree as one passes from grade 1 to grade 3 cirrhotic change. In the age period 50 to 79 years the percentage distribution within each type is as follows: grade 1 cirrhosis, 32.7 per cent latent and 10.6 per cent

active; grade 2 cirrhosis, 23 per cent latent and 16.1 per cent active; grade 3 cirrhosis, 9.6 per cent latent and 39.7 per cent active. If one considers grade 3 cirrhosis in the period of from 40 to 69 years of age, one sees that here will be found 18.1 per cent of the cases of the latent type and 47.1 per cent of the cases of the active type. This appears to indicate that latent cirrhosis does not tend to progress into the active form. The latent type either progresses more slowly or tends to become arrested. It is also apparent that in latent cirrhosis there is often a lower degree of microscopic change than in the active form; 75.8 per cent of the cases of latent cirrhosis showed grade 1 or 2 change, whereas 62.6 per cent of those of active cirrhosis showed grade 3 change.

Table 3 carries this analysis one step further. In this table it appears that in the first two degrees the percentage distributions for corresponding decades agree fairly well, but that agreement is not present in third degree cirrhosis. It is to be noted that 40 per cent of the 230 cases in which a definite age was given are found in the grade 3 active group, whereas only 8 per cent fall within the grade 3 latent group.

The foregoing findings indicate that the degree of cirrhosis is one of the factors in latency, although many patients who suffer from the disease have only a mild degree of cirrhotic change. Further, it appears that high degrees of cirrhosis are but rarely unaccompanied by symptoms.

After these tabulations were made in all cases classed as grade 1 the sections were reexamined to determine whether the presence of so-called adenomas could be responsible for the fact that so many cases had been placed in this group. Reexamination showed that in 2 cases of active cirrhosis and in 1 of latent cirrhosis such a relobulation was present. In the remainder no evidence of adenoma was found. Thus it appeared that regeneration was responsible for neither the slight degree of microscopic change nor the latency of the disease.

OBSERVATIONS ON THE WEIGHT OF THE LIVER

The microscopic changes in the cirrhotic livers having shown such great variations, a study was made of the weights of the livers, since not all could be examined grossly. A tabulation of these weights is shown in table 4. (Boyd,¹¹ using the records of this laboratory, recently reported on the weight of the normal liver and of the normal spleen. She showed that there is a significant difference in weight according to sex and also that these organs decrease in weight with advancing age. The normal averages for the various decades used in this table were furnished by her.) From this table it appears that, although there is

11. Boyd, E.: Arch. Path. **16**:350, 1933.

considerable variation in each decade between the maximum and minimum weights of cirrhotic livers, there is a decided decrease in the maximum and average weights with advancing age. It is to be noted that the weight of the liver decreases with age in the normal cases also. The decrease in the average weights for the successive decades in the latent cases in males shows no great variation from the normal. In some of the decades the cases are so few that no conclusion can be drawn. The decrease in weight with advancing age is decidedly greater in the cases of active cirrhosis than in the normal group. In the fourth, fifth and sixth decades in the cases of the latent group and in the fourth and fifth decades in the cases of the active group there may be a signifi-

TABLE 4.—*Comparison of the Weights of Cirrhotic Livers with the Normal Averages According to Sex, Age and Maximum, Minimum and Average Weight (Gm.)*

Age, Years	Males					Females				
	No. of Cases	Maximum Weight	Minimum Weight	Average Weight	Boyd's Normal Average	No. of Cases	Maximum Weight	Minimum Weight	Average Weight	Boyd's Normal Average
Latent Cirrhosis										
20-29	4	1,700	1,185	1,332	1,838	1,437
30-39	5	2,922	1,380	2,156	1,872	1,462
40-49	11	3,530	1,250	2,156	1,888	2	1,601	1,390	1,495	1,570
50-59	18	3,792	1,050	1,996	1,848	3	2,800	1,592	2,097	1,464
60-69	15	2,713	720	1,729	1,728	3	2,100	1,390	1,780	1,400
70-79	9	2,100	1,007	1,419	1,426	1,263
80-89	2	1,650	1,500	1,575	1	987	987
Active Cirrhosis										
20-29	2	1,550	1,400	1,475	1,838	2	3,025	2,560	2,792	1,437
30-39	11	3,080	1,097	2,092	1,872	7	3,140	875	1,751	1,462
40-49	16	3,400	940	1,999	1,888	6	3,100	880	2,144	1,570
50-59	29	2,500	750	1,452	1,848	8	2,391	650	1,282	1,464
60-69	22	2,500	750	1,305	1,728	10	1,625	675	1,130	1,400
70-79	15	2,100	675	1,365	1,426	5	1,100	625	767	1,263
80-89

cant increase in the weights of cirrhotic livers in males. This analysis does not entirely confirm Rolleston and McNee's ⁴⁰ statement that there is a decrease in the size of cirrhotic livers with advancing age.

The following data do not appear in the table. In the latent group only 2 patients, 1 male and 1 female, had livers weighing less than 1,000 Gm. In the active group, on the other hand, 16.5 per cent of the males and 43.5 per cent of the females had livers weighing 1,000 Gm. or less. It is unlikely that this high incidence of very small livers found in females with active cirrhosis can be attributed entirely to sex, which agrees with Rolleston and McNee's ⁴⁰ statement that "sex does not exert any very special influence on the weight of the cirrhotic liver."

In figure 2, the weights of the livers in the cases of latent cirrhosis have been plotted on the standard of normal variability in the weight of the liver, constructed by Boyd, in which the dispersion of normal weights is divided into the eight zones indicated. The number of

weights which normally should fall below any given line is indicated in percentages at the end of each line, and the number expected in each zone would be the difference between its limiting percentile lines. The number of weights of cirrhotic livers found in each of the eight zones is shown in percentages in table 5. A count of the numbers of weights in each of the eight zones shows that 13.6 per cent are found above the 97.5 percentile line, where only 2.5 per cent are expected normally, and, likewise, that 13.6 per cent are below the 2.5 percentile line. Apparently the liver may be either hypertrophied or atrophied. This conclusion is supported by finding that such deviations in normal weights from the expected standard would not occur by chance alone once in a million times, since *Chi-square* is 91.5 and *P* is 0.000000 (Boyd¹¹).

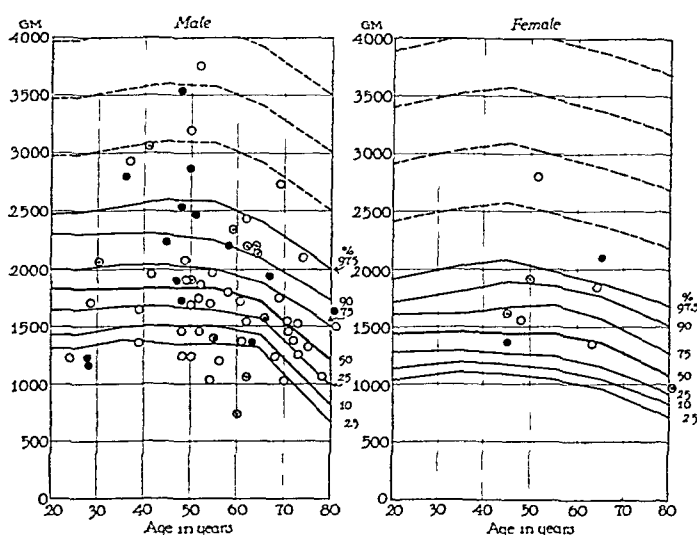


Fig. 2.—Dispersion of the weights of the livers in the cases of latent cirrhosis, plotted on the standard of normal variability in weight. In this and in the following charts the white circles indicate grade 1 cirrhosis, the white circles with the black centers, grade 2, and the black circles, grade 3.

Inspection of the graph indicates that in latent cirrhosis the liver tends to be hypertrophied oftener in the early decades of adult life and atrophied oftener in the later decades. Therefore the incidence of weights was divided into two groups at 50 years of age. This division shows that the percentage of weights above and below the probable limits of normal variation remains equal in both groups: it is 17.4 for the period of from 20 to 49 years and 12 for the period of from 50 to 89 years. Here again, the liver may be hypertrophied or atrophied, regardless of age. This statement is supported by finding that such deviations in normal weights from the expected standard would not occur by chance alone once in a million times, since in the earlier decades *Chi-square* is 45.6 and *P* is 0.000000, and in the later decades *Chi-square* is 57.7 and *P* is 0.000000.

TABLE 5.—Comparison of the *W* weights of Cirrhotic Liceers with the Normal Standard *

	Number of Weights (Both Sexes)	Percentage of Weights Between the Percentile Lines												Percentage of Weights	
		Above 97.5 Line						Below 2.5 Line						Above 50 Line	Below 50 Line
		97.5	90	75	50	25	2.5	97.5	90	75	50	25	2.5		
Percentage of weights expected.....	..	2.5	7.5	15	25	25	75	7.5	15	25	25	75	7.5	50	50
Latent cirrhosis	73	13.6	15.0	8.2	16.1	20.5	2.7	9.5	13.6	8	91.5	0.000000	53.4	46.5	
20-49 years	{23	17.4	4.3	13.0	21.7	13.0	4.3	8.6	17.4	8	45.6	0.000000	56.5	43.4	
50-89 years	{50	12.0	20.0	6.0	11.0	21.0	2.0	10.0	12.0	8	57.7	0.000000	52.0	48.0	
Active cirrhosis	133	12.0	8.2	4.5	13.5	9.7	6.0	9.0	36.8	8	716.3	0.000000	33.3	61.6	
20-49 years	{41	31.8	15.9	2.2	11.3	4.5	9.0	6.8	18.1	8	215.2	0.000000	61.3	38.6	
50-89 years	{89	2.2	4.4	5.6	11.6	12.3	4.1	10.1	16.0	8	638.9	0.000000	26.9	73.0	
Percentage of weights expected.....	..	Above 75 Line						Below 25 Line						50	50
Latent cirrhosis	73	25	36.9	16.1	20.5	20.5	25	25	25	1	6.9	0.07	53.1	46.5	
20-49 years	{23	31.7	13.0	21.7	13.0	13.0	30.1	3.4	3.4	4	5.8	0.10	56.5	43.1	
50-89 years	{50	38.0	21.0	11.0	21.0	21.0	21.0	21.0	21.0	4	5.8	0.10	52.0	48.0	
Active cirrhosis	133	21.8	13.5	13.5	9.7	9.7	51.8	51.8	51.8	4	57.9	0.000000	33.3	61.6	
20-49 years	{11	50.0	11.3	11.3	4.5	4.5	31.0	31.0	31.0	1	23.6	0.000025	61.3	38.6	
50-89 years	{89	12.3	11.6	11.6	12.3	12.3	60.6	60.6	60.6	4	60.3	0.000000	26.9	73.0	
Percentage of weights expected.....	..	Above 50 Line						Below 50 Line						50	50
Latent cirrhosis	73	50	53.4	46.5	46.5	46.5	50	50	50	2	0.31	0.60	53.1	46.5	
Active cirrhosis	133	38.3	61.6	61.6	61.6	61.6	38.3	38.3	38.3	2	7.2	0.01	38.3	61.6	
20-49 years	{11	61.3	38.6	38.6	38.6	38.6	61.3	61.3	61.3	2	2.2	0.10	61.3	38.6	
50-89 years	{89	26.9	73.0	73.0	73.0	73.0	26.9	26.9	26.9	2	18.8	0.000000	26.9	73.0	

* Sex has been eliminated in this table, since the cases found in the corresponding zones may be added together without introducing an error.

† When less than ten weights are expected in a zone the interpretation of the χ^2 tests is not highly reliable.

As the samples are so small that less than ten weights are expected normally in the extreme zones, the counts were grouped first into the four quartiles and then into the number above and below the median line (table 5).

The count of the number of weights in the quartiles for the total age period and its two divisions indicates that a disproportionate number of weights are in the upper quartile (36.9, 34.7 and 38 per cent) and about the expected number are in the lower quartile (26, 30.4 and 24 per cent), but the Chi-square values 6.9, 3.4 and 5.8 are so low that these differences could occur by chance alone 7, 40 and 10 times, respectively, in a hundred. In short, about the usual number of weights are in the two middle quartiles, and the usual number are outside. However, this test

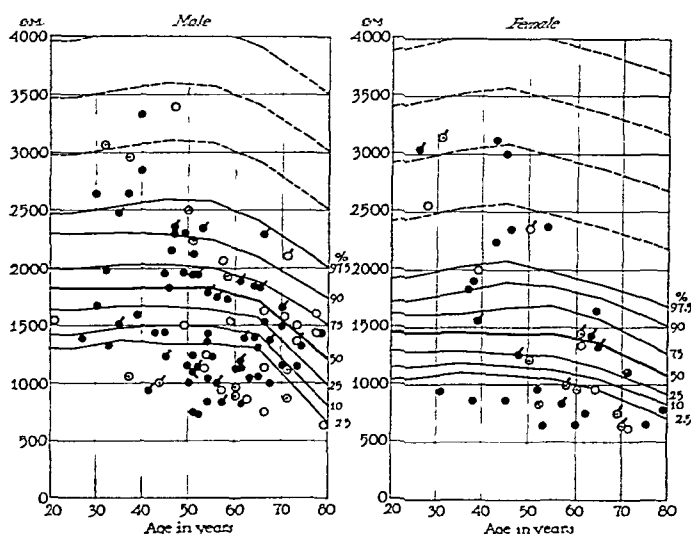


Fig. 3.—Dispersion of the weights of the livers in the cases of active cirrhosis, plotted on the standard of normal variability in weight. The circles with the dashes indicate the cases in which hemorrhage occurred.

gives no indication of how far the weights in the fourth quartile are above the 75 percentile line or how far those in the first quartile are below the 25 per centile line. Likewise, since the numbers below and above the median line, 53.4 and 46.5 per cent, could occur by chance 60 times in one hundred, this dispersion is obviously not different from the number of normal weights above and below the median. Therefore the number of hypertrophied and atrophied livers counterbalance each other so that the median weight in latent cirrhosis is not significantly different from that of the normal liver.

The weights of the livers in the cases of active cirrhosis were plotted on the normal standard (fig. 3). The count of the number of weights in each of the eight zones shows that 12 per cent are above the 97.5 percentile line and 36.8 per cent are below the 2.5 percentile line, when in each case only 2.5 per cent are to be expected normally (table 5). As

in latent cirrhosis, the liver may be hypertrophied or atrophied. Support for this conclusion is found in the fact that such deviations in normal weights from the expected standard would not occur by chance once in a million times, since Chi-square is 716 and P is 0.000000.

Examination of the graph indicates that in active cirrhosis the liver tends to be hypertrophied oftener in the early decades of adult life and atrophied oftener in the later decades. As in latent cirrhosis, the incidence of weights in active cirrhosis was divided into two groups at the age of 50 years. This division shows that for the age period of from 20 to 49 years 31.8 per cent of the weights are above and 18.1 per cent are below the probable limits of normal variation, instead of the expected 2.5 per cent. (It is to be noted that 17.4 per cent of the weights in latent cirrhosis in this age period were also found below the 2.5 percentile line.) It appears that in the earlier decades active cirrhosis may be accompanied by a hypertrophic or an atrophic liver, but that hypertrophy is to be expected rather than atrophy. This conclusion is supported by finding that such deviations in normal weights from the expected standard would not occur by chance once in a million times, since Chi-square is 215 and P is 0.000000. For the age period 50 to 89 years, the weights are 2.2 per cent above and 46 per cent below the probable limits of normal variation, where 2.5 per cent are expected normally. In other words, the normal number occur above the 97.5 percentile line, and a markedly disproportionate number fall below the 2.5 percentile line. Whereas a hypertrophic liver may be found in active cirrhosis in the later decades, atrophy is rather to be expected. Support for this statement is found in the fact that such deviations in normal weights from the expected standard would not occur by chance once in a million times, since Chi-square is 689.

The count of weights in active cirrhosis by quartiles for the total age period shows 24.8 per cent, or the normal number, in the upper quartile and a markedly disproportionate number, 51.8 per cent, in the lower quartile (table 5). This indicates that in active cirrhosis no more than the normal number of relatively large livers are to be found, but that relatively small livers are the rule. This is borne out by finding that this difference would not occur by chance alone once in a million times, since Chi-square is 57.9.

From the count of weights by quartiles for the age period from 20 to 49 years, it appears that a disproportionate number of weights are in the upper (50 per cent) and lower (34.0 per cent) quartiles (table 5). In this age period both more relatively large and more relatively small livers are found than would be expected from chance, since Chi-square is 23.6 and the larger weights predominate.

From the count of weights by quartiles for the age period from 50 to 89 years it is indicated that a disproportionately small number, 12.3 per

cent, are in the upper and a disproportionately large number, 60.6 per cent, are in the lower quartile, i. e., less than the normal number of relatively large livers and more than the normal number of relatively small livers (table 5). Whereas relatively large livers may sometimes be found after the age of 50 years, relatively small livers are the rule.

A disproportionate number, 61.6 per cent, of the weights of active cirrhotic livers are below the median line (table 5). In other words, in active cirrhosis the weights in approximately three fifths of the cases fall below the median line. Small livers rather than large are the rule in active cirrhosis. In the early decades, before 50 years, 61.3 per cent are above the median line, which could occur by chance 10 times in a hundred. In the later decades, after 50 years, 73 per cent are below the median line, which could not occur by chance once in a million times.

From these various analyses it appears that in the earlier decades active cirrhosis tends to be accompanied by hypertrophy of the liver and that in the later decades it is unquestionably accompanied by atrophy. Herein may lie the explanation of the origin of the terms hypertrophic cirrhosis and atrophic cirrhosis; in the young, hypertrophy is to be expected, and in the old, atrophy. Rolleston and McNee^{4a} found the same tendency toward atrophy with advancing age, but apparently failed to recognize that the enlargement in latent cases might be due to differences in age.

In figures 2 and 3 the degree of microscopic change in each liver is shown by an appropriate mark. Inspection of these graphs indicates that in any degree of cirrhosis, whether active or latent, the liver may be large or small. It also appears that large or small cirrhotic livers may be accompanied by a slight or a pronounced degree of microscopic change. A comparison of the weights of the livers in latent and active cirrhosis, according to the degree of microscopic change, is shown in table 6. In this table it may be seen that in all degrees of cirrhosis, whether latent or active, disproportionate numbers are found above the 97.5 percentile line and below the 2.5 percentile line. In latent cirrhosis the various degrees of microscopic change are more or less equally represented by hypertrophy and atrophy, but in active cirrhosis the tendency toward atrophy is more definite. A comparison of latent and active cirrhosis in each degree of microscopic change shows that in grade 1 cirrhosis the difference could occur by chance 28 times in a hundred, since Chi-square is 5.5 and P is 0.28; hence no significant difference is demonstrable (Dunn¹²). However, in grade 2 cirrhosis the difference could occur only 17 times in a thousand, since Chi-square is 12.3 and P is 0.017, and so it is significant. Similarly, in grade 3 cirrhosis

12. Dunn, H. L.: *Physiol. Rev.* 9:275, 1929.

the difference could occur by chance only 4 times in a hundred, since Chi-square is 10.3 and P is 0.04, and is significant.

Considering all livers below the 2.5 percentile line as atrophic, a comparison was made between the proportion of these livers occurring in latent and active cirrhosis according to the degree of cirrhosis and the group as a whole (table 7). Since the difference between the proportion of atrophic livers with grade 1 cirrhosis in the latent and active

TABLE 6.—Comparison of the Incidence of the Weights of the Livers in Latent and Active Cirrhosis According to the Degree of Cirrhosis, Plotted on the Normal Standard

	Number of Weights (Both Sexes)	Percentages of Weights Between Percentile Lines					n'	χ^2	P	Percentage of Weights	
		Above 97.5 Line	97.5 to 75	75 to 25	25 to 2.5	Below 2.5 Line				Above 50 Line	Below 50 Line
Percentage of weights expected.....	..	2.5	22.5	50	22.5	2.5	50	50
Grade 1.....	45										
Latent type.....	{29	10.3	0	58.6	15.7	17.2	5	3.3	0.28	54.4	65.5
Active type.....	{16	12.5	12.5	21.2	18.7	25.0				43.7	56.2
Grade 2.....	57										
Latent type.....	{28	10.7	39.2	24.9	14.2	10.7	5	12.3	0.017	64.2	35.7
Active type.....	{29	13.7	13.7	13.7	10.3	48.2				34.4	65.5
Grade 3.....	104										
Latent type.....	{16	25.0	37.5	18.7	6.2	12.5	5	10.3	0.040	68.7	31.2
Active type.....	{88	11.3	12.5	24.9	15.9	35.2				38.6	61.3

TABLE 7.—Percentage of Atrophic Livers According to Degree of Cirrhosis in Latent and Active Types

	Latent Cases, Percentage	Active Cases, Percentage	Difference	R	P
Grade 1.....	17.24 \pm 7.01	25.0 \pm 10.8	7.76 \pm 12.89	0.6	0.55
Grade 2.....	10.71 \pm 5.86	48.27 \pm 9.33	37.56 \pm 10.96	3.42	0.00067
Grade 3.....	12.5 \pm 8.26	35.22 \pm 5.09	22.72 \pm 9.71	2.33	0.016
All grades.....	13.69 \pm 4.02	36.84 \pm 4.18	23.15 \pm 5.803	3.98	0.000033

groups is only 0.6 times its standard error, the difference is not significant. But the differences between the proportion in latent and active grade 2 cirrhosis, in latent and active grade 3 cirrhosis and in latent and active cirrhosis as a whole are significant, since they are 3.4, 2.3 and 3.9 times their standard errors, respectively; i. e., they would occur by chance alone 67 times in a hundred thousand, 16 times in a thousand and 6 times in a hundred thousand, respectively. If a large enough series of cases of cirrhosis with grade 1 microscopic change were available, it is possible that a difference might be demonstrable between the latent and active types in which the livers were atrophic, but this is not

likely. There is a demonstrable difference in the incidence of atrophy of the liver in the latent and active types when more marked microscopic changes are present. The same is true when the severity of the process is disregarded and the two types are compared.

These analyses suggest that the size of the liver and the degree of microscopic change are not responsible for the clinical signs of activity, but that the activity of the cirrhotic process is responsible for the size of the liver and the degree of microscopic change.

Since hemorrhage may exert an influence on the weight of the liver, the patients who died of active cirrhosis and who had hemorrhage are

TABLE 8.—*Comparison of the Weights of Spleens in Cirrhosis with Normal Averages According to Sex, Age and Maximum, Minimum and Average Weights*

Decades	Males					Females				
	Number of Cases	Maximum Weight	Minimum Weight	Average Weight	Boyd's Normal Average	Number of Cases	Maximum Weight	Minimum Weight	Average Weight	Boyd's Normal Average
Latent Cases										
20-29.....	3	570	180	313	204	168
30-39.....	5	800	154	352	168	164
40-49.....	10	670	57	259	179	2	500	255	377	172
50-59.....	17	463	70	227	127	3	600	300	400	133
60-69.....	17	462	75	211	132	3	425	270	332	129
70-79.....	9	400	85	205	123	121
80-89.....	2	450	100	275	...	1	...	77	77	81
Average.....				236					320	
Active Cases										
20-29.....	2	510	335	423	204	2	300	250	275	168
30-39.....	12	925	110	483	168	5	590	190	384	164
40-49.....	16	1,035	50	297	179	7	470	125	263	172
50-59.....	28	2,060	70	412	127	8	980	160	419	133
60-69.....	23	875	92	356	132	9	600	140	299	129
70-79.....	13	855	70	282	123	5	300	100	199	121
80-89.....	81
Average.....				391					317	

indicated by a dash from the respective marks (fig. 3). From inspection of this graph, hemorrhage does not appear to be an important factor in the decrease in the weight of the liver in the active cases of cirrhosis in this series. As Boyd found that in normal persons who died of acute hemorrhage the livers weighed significantly less than in normal persons who died as a result of accidents without hemorrhage, a comparison was made between the weights of the livers in active cirrhosis with and without hemorrhage. No significant difference could be demonstrated.

OBSERVATIONS ON THE WEIGHT OF THE SPLEEN

A somewhat similar study was made of the weights of the spleens in this series of cases of cirrhosis of the liver, but no microscopic examination of the spleens was made.

Table 8 shows a comparison of the weights of the spleens with the normal averages obtained by Boyd. From this table it appears that while there is a great variation in weights, nevertheless, in both latent and active cirrhosis, especially in the latter, the spleen tends to be enlarged. Normally the spleen decreases in weight with advancing age, but there is no definite evidence of any such tendency when active cirrhosis of the liver is present. There is a reduction in the averages in the male with advancing age, but the average is still much higher

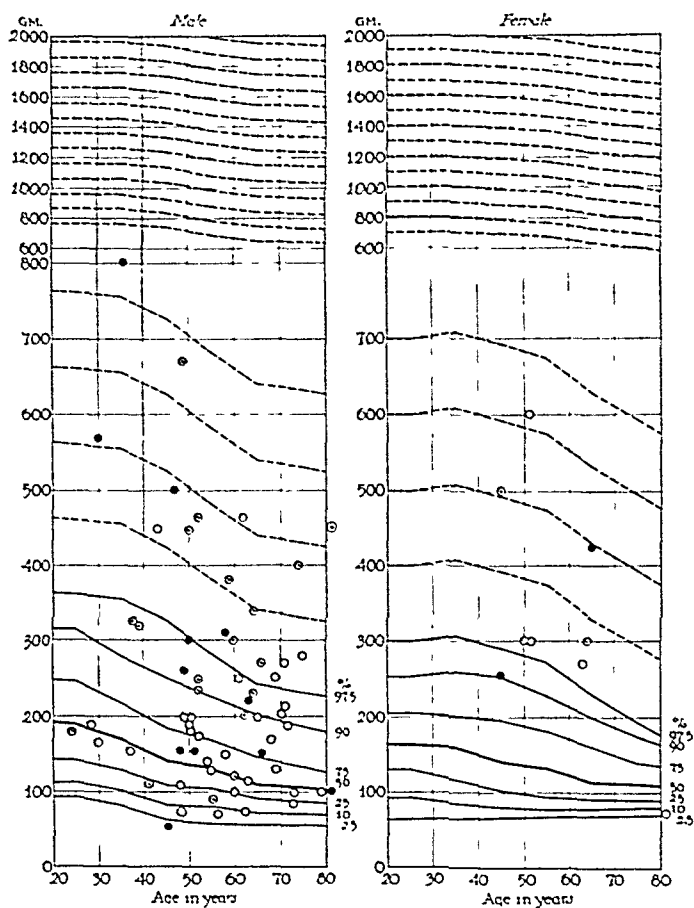


Fig. 4.—Dispersion of the weights of the spleens in the cases of latent cirrhosis of the liver plotted on the standard of normal variability in weight.

than the normal average for the corresponding decades. It is to be noted that quite small spleens may be found in both latent and active cases of cirrhosis of the liver.

To carry the analysis further, the weights of the spleens were plotted on the standard of normal variability in weight of the spleen constructed by Boyd (figs. 4 and 5). The number of weights found in each of the eight zones is shown in percentages in table 9. In these graphs the tendency to enlargement of the spleen, whether the cirrhosis of the liver is latent or active, is obvious. Although some

patients with cirrhosis of the liver have very small spleens, as a rule a person with active cirrhosis has a larger spleen than a person with latent cirrhosis.

In table 9 in each instance the disproportionately large numbers of weights above the 97.5 percentile line, the 75 percentile line and the 50 percentile line are obvious. In each instance this disproportion is more marked in active than in latent cirrhosis. The disproportionately

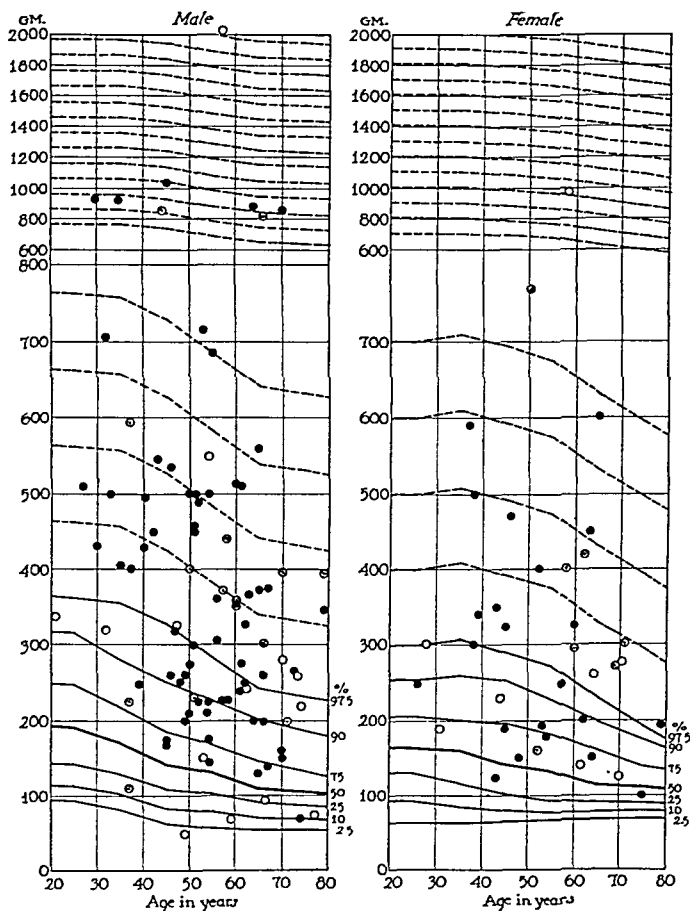


Fig. 5.—Dispersion of the weights of the spleens in the cases of active cirrhosis of the liver, plotted on the standard of normal variability in weight.

small number of weights below the 2.5 percentile line, the 25 percentile line and the 50 percentile line is also very striking. It may be seen that, regardless of how the weights of the spleens in active and latent cirrhosis of the liver are grouped, with but 1 exception the chances that the differences found were due to sampling alone are less than 1 in a million. In all cases the differences are significant. The almost constant enlargement of the spleen in cirrhosis of the liver, whether active or latent, makes one wonder which organ is involved first by the process.

TABLE 9.—*Comparison of the Weights of the Spleens in Cirrhosis of the Liver with the Normal Standard **

	Number of Weights (Both Sexes)	Percentage of Weights Between Percentile Lines										P	χ^2	Percentage of Weights	
		Percentage of Weights Between Percentile Lines												Above 50 Line	Below 50 Line
		Above 97.5 Line	97.5 to 90	90 to 75	75 to 50	50 to 25	25 to 10	10 to 2.5	2.5 to Below 2.5 Line	Below 2.5 Line					
Percentage of weights expected.....	..	2.5	7.5	15	25	25	15	7.5	2.5	2.5	50	50
Latent cirrhosis	72	31.7	16.6	13.8	12.5	11.1	5.5	4.1	1.3	1.3	0.000000	8	322.6	77.7	22.2
20-49 years	{20	30.0	20.0	5.0	10.0	20.0	5.0	5.0	5.0	5.0	0.000000	8	62.9	65.0	35.0
50-89 years	{52	33.5	15.3	17.3	13.5	7.6	5.6	3.8	0.0	0.0	0.000000	8	161.3	82.6	17.3
Active cirrhosis	130	59.2	11.5	12.3	10.7	2.3	2.3	0.7	0.7	0.7	0.000000	8	1,737.7	93.8	6.1
20-49 years	{14	59.0	11.3	11.3	11.3	2.2	2.2	0.0	2.2	2.2	0.000000	8	585.3	93.1	6.8
50-89 years	{86	53.3	11.6	12.7	10.1	2.3	2.3	1.1	0.0	0.0	0.000000	8	1,153.0	91.1	5.8
Percentage of weights expected.....	..	Above 75 Line										Below 25 Line			
		25		75 to 50		50 to 25		Below 25 Line							
Latent cirrhosis	72	65.2		12.5		11.1		11.1				4	62.3	77.7	22.2
20-49 years	{20	55.0		10.0		20.0		15.0				4	10.0	65.0	35.0
50-89 years	{52	69.2		13.5		7.6		9.6				4	61.9	82.6	17.3
Active cirrhosis	130	83.0		10.7		2.3		3.8				4	235.9	93.8	6.1
20-49 years	{14	81.8		11.3		2.2		4.5				4	76.5	93.1	6.8
50-89 years	{86	83.7		10.1		2.3		3.4				4	159.1	91.1	5.8
Percentage of weights expected.....	..	Above 50 Line										Below 50 Line			
		50		50		50		50							
Latent cirrhosis	72	77.8		22.2		22.2		22.2				2	22.2	77.7	22.2
Active cirrhosis	130	93.8		6.1		6.1		6.1				2	103.0	93.8	6.1

* Sex has been eliminated in this table, since the cases found in the corresponding zones may be added without introducing an error.

A comparison has been made of the weights of the spleens according to the degree of cirrhosis which was present in the livers (table 10). It appears that in both latent and active cirrhosis high degrees of microscopic change in the liver tend to be accompanied by a larger spleen than is the case with slighter changes in the liver, and, further, that the spleen tends to be larger in active than in latent cirrhosis. A comparison of the weights of the spleens in corresponding degrees

TABLE 10.—*Comparison of the Relation of the Weights of the Spleen in Cirrhosis of the Liver with the Normal Standard, According to the Degree of Cirrhosis of the Liver in the Latent and Active Types*

	Number of Weights (Both Sexes)	Percentage of Weights Between the Percentile Lines					n'	χ^{2*}	P	Percentage of Weights	
		Above 97.5 Line	97.5 to 75	75 to 25	25 to 2.5	Below 2.5 Line				Above 50 Line	Below 50 Line
Percentage of weights expected.....	..	2.5	22.5	50	22.5	2.5	50	50
Grade 1 cirrhosis.....	47										
Latent type.....	{30	23.3	33.3	29.9	13.3	0	5	7.0	0.13	73.2	26.5
Active type.....	{17	52.9	23.4	11.6	5.8	5.8				82.3	17.6
Grade 2 cirrhosis.....	55										
Latent type.....	{28	46.4	24.9	17.7	10.6	0	5	1.6	0.8	74.9	24.8
Active type.....	{27	62.9	14.8	14.8	7.4	0				92.5	7.4
Grade 3 cirrhosis.....	100										
Latent type.....	{14	35.7	35.6	21.4	0	7.1	5	7.2	0.13	92.7	7.1
Active type.....	{86	59.3	26.7	12.7	1.1	0				96.4	3.4

* Determined by the Chi-square technic for comparing two observed distributions (Dunn).

TABLE 11.—*Percentage of Hypertrophied Spleens According to the Degree of Cirrhosis of the Liver in the Latent and Active Types*

	Latent Type, Percentage	Active Type, Percentage	Difference	R	P
Grade 1.....	23.33 \pm 7.72	52.94 \pm 12.11	29.61 \pm 14.35	2.06	0.01
Grade 2.....	46.42 \pm 9.04	62.96 \pm 9.29	16.54 \pm 13.23	1.25	0.211
Grade 3.....	35.71 \pm 12.81	59.3 \pm 5.29	23.59 \pm 13.85	1.70	0.089
All grades.....	34.72 \pm 5.61	59.23 \pm 5.19	24.51 \pm 7.64	3.20	0.0014

of sclerotic change in the liver shows no demonstrable difference, since in the three degrees these differences could occur by chance as often as 13, 80 and 13 times in a hundred.

Considering all spleens above the 97.5 percentile line as hypertrophic, a comparison was made between the proportion of these spleens occurring in latent and active cirrhosis according to the degree of cirrhosis of the liver and the group as a whole (table 11). The difference between the proportions must be at least twice its standard error to be significant. It appears that there is a possibly significant difference

between latent and active grade 1 cirrhosis and that a significant difference is not demonstrable in grade 2 and grade 3 cirrhosis. However, when the degree of microscopic change in the liver is disregarded, there is a definitely significant difference in the weights of the hypertrophied spleens in latent and active cirrhosis, since the differences found could be due to sampling only 14 times in ten thousand. Comparison between the weights of the hypertrophied spleens by degree in each type of cirrhosis shows no demonstrable difference.

TABLE 12.—*Causes of Death in Hepatic Cirrhosis*

Latent Cases		Active Cases	
Heart disease.....	22	Cirrhosis.....	74
Accident.....	12	Hemorrhage.....	18
Peritonitis.....	5	Peritonitis.....	12
Pneumonia.....	5	Peritonitis (tuberculous).....	2
Pulmonary tuberculosis.....	4	Heart disease.....	6
Cerebral hemorrhage.....	4	Pneumonia.....	5
Meningitis.....	3	Accident.....	4
Diabetes mellitus.....	3	Carcinoma (stomach).....	3
Carcinoma (stomach).....	3	Cerebral hemorrhage.....	3
Alcoholism.....	3	Strangulated hernia.....	3
Carcinoma (colon).....	3	Carcinoma (liver).....	3
Wilson's disease.....	2	Pulmonary abscess.....	3
Pericarditis.....	2	Sepsis.....	3
Encephalomalacia.....	2	Alcoholism.....	3
Gunshot wounds.....	2	Enteritis.....	3
Carbon monoxide poisoning.....	2	Postoperative shock.....	2
Suppurative pancreatitis.....	1	Miliary tuberculosis.....	1
Suppurative cholecystitis.....	1	Chronic nephritis.....	1
Pulmonary abscess.....	1	Syphilis.....	1
Syphilis.....	1	Postoperative hemorrhage.....	1
Empyema.....	1	Diphtheria.....	1
Strangulated hernia.....	1	Carcinoma (colon).....	1
Carcinoma (prostate).....	1	Burn.....	1
Pulmonary embolism.....	1	Carcinoma (hepatic duct).....	1
Heat stroke.....	1	Carcinoma (prostate).....	1
Carcinoma (cervix).....	1	Mesenteric thrombosis.....	1
		Pernicious anemia.....	1
		Pericarditis.....	1
		Purpura.....	1
		Erysipelas.....	1
		Hodgkin's disease.....	1
		Starvation.....	1
		Sudden death.....	1

CAUSES OF DEATH

Table 12 sets forth the causes of death in the two groups and shows that a great variety of conditions were responsible for death. Heart disease was the major cause of death in the cases in the latent group, but was the cause of death in but a comparatively small number of the cases of active cirrhosis. The 5 cases of peritonitis in the latent series resulted from carcinoma of the gastro-intestinal tract in 3 cases, pelvic abscess in 1 case and duodenal ulcer in 1 case. Attention should be called to the low incidence of tuberculous peritonitis (2 cases), since the statement has been made that it occurs in 10 per cent of all cases of cirrhosis. In this series its incidence is less than 1 per cent.

CONCLUSIONS

Two hundred and forty-five cases of portal cirrhosis found in routine postmortem examinations of the bodies of 11,912 adults are reported. This is an incidence of 2.05 per cent. No patient for whom an exact age was given was over 89 years of age, and only 1 patient in the active group was over 80 years of age.

Of these cases, 64.4 per cent are considered as active and 35.5 per cent as latent.

The corrected ratio of males to females in the latent group is 3.5:1, and in the active group, 1.1:1. This shows practically no difference in the sex incidence of the disease in patients who had had symptoms of cirrhosis. It bears out the statements of Yeld and of Rolleston and McNee that cirrhosis is latent more often in males.

The distribution of active and latent cirrhosis according to decades of life is practically identical; approximately 70 per cent of the cases occurred in persons between the ages of 40 and 69 years.

Persons with latent cirrhosis tend to have a less advanced cirrhotic process than is found in the active group.

In cirrhosis the dispersion of the weights of the livers is increased both above and below normal limits. This is more marked in active than in latent cirrhosis. In active cirrhosis there are a disproportionately large number of hypertrophic livers in the earlier decades of adult life and a disproportionately large number of atrophic livers in the later decades.

Livers which show the more advanced degrees of cirrhosis tend to be smaller than those in which the process is less advanced. This is particularly true of those which have given rise to symptoms.

Hemorrhage as a cause of the decreased weight is apparently unimportant.

The spleen is usually markedly enlarged in cirrhosis of the liver, and the enlargement is more frequent in the active than in the latent cases.

Heart disease is the most frequent cause of death in latent cirrhosis, but is a relatively infrequent cause in active cirrhosis.

EFFECT OF ROENTGEN IRRADIATION ON THE HEALING OF WOUNDS

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In conducting an investigation on the effect of roentgen rays on the healing of wounds, Dr. E. A. Pohle and I obtained certain striking results. These have been reported in the radiologic literature,¹ but the pathologic observations are deemed of sufficient interest for publication in more detail.

METHODS

White rats of the same strain and of approximately uniform size were used. These animals were chosen as they were available in large numbers and easily cared for. A single dose of 1,000 roentgens was given in each instance. In the first set of these experiments,^{1a} it was found that results did not vary with the quality of radiation; accordingly, the following type of irradiation was used in the experiments to be discussed here: 100 kilovolts, 2 mm. aluminum, 20 cm. focal skin distance, effective 0.34 angstrom (transmitted through 2 mm. aluminum, 0.7 roentgen per second).

Seventy-eight animals were used, and in each a wound approximately 6 cm. long was made in the skin of the back, one Michel clip being applied to prevent excessive gaping. Metaphen was used as a disinfectant. One half of each wound was treated, the other half being left as a control. Irradiation was done in one group immediately, in another twenty-four hours after incision, and in a third, forty-eight hours after incision, the rats falling into three general groups according to the interval between cutting and exposure. The progress of healing was traced by daily stages, rats in each general group being killed from one to nine days after incision. The tissues were fixed in a trinitrophenol formaldehyde solution,² embedded in paraffin and stained with hematoxylin and eosin and with hematoxylin and van Gieson's stain. Twelve of the seventy-eight animals were discarded on account of infection of the wounds, so that this report is in reality based on the results found in sixty-six animals.

RESULTS

In the reporting of results, the animals naturally fall into the three general groups indicated. Since the effect of irradiation was in principle the same in all groups and differed in different animals only in degree, this effect will be discussed first in general, and quantitative considerations will be taken up later.

From the departments of pathology and radiology, University of Wisconsin.

1. (a) Pohle, E. A.; Ritchie, G., and Wright, C. S.: *Radiology* **16**:445, 1931.
(b) Pohle, E. A., and Ritchie, G.: *ibid.* **20**:102, 1933.

2. Bouin's solution is composed of the following: solution of formaldehyde, U. S. P., 500 cc.; distilled water, 1,500 cc.; glacial acetic acid, 100 cc.; trinitrophenol to saturation point.

Three chief effects were noted: (1) retardation of fibroblastic growth; (2) a change in the fibroblastic development, with the production of abnormal cells, and (3) the formation of a fibrin network, poor in cells, which persisted in many cases beyond the usual time for such an exudate.

1. The first of these, the retardation of growth, was the most striking and the most important phenomenon to be seen. It was present to a great degree in some animals, in which the irradiated portion of the wound showed absolutely barren margins with apparently no attempt at healing, while in the control portion complete closure by an abundant fibroblastic growth supervened (fig. 1). Apparently the scavenger

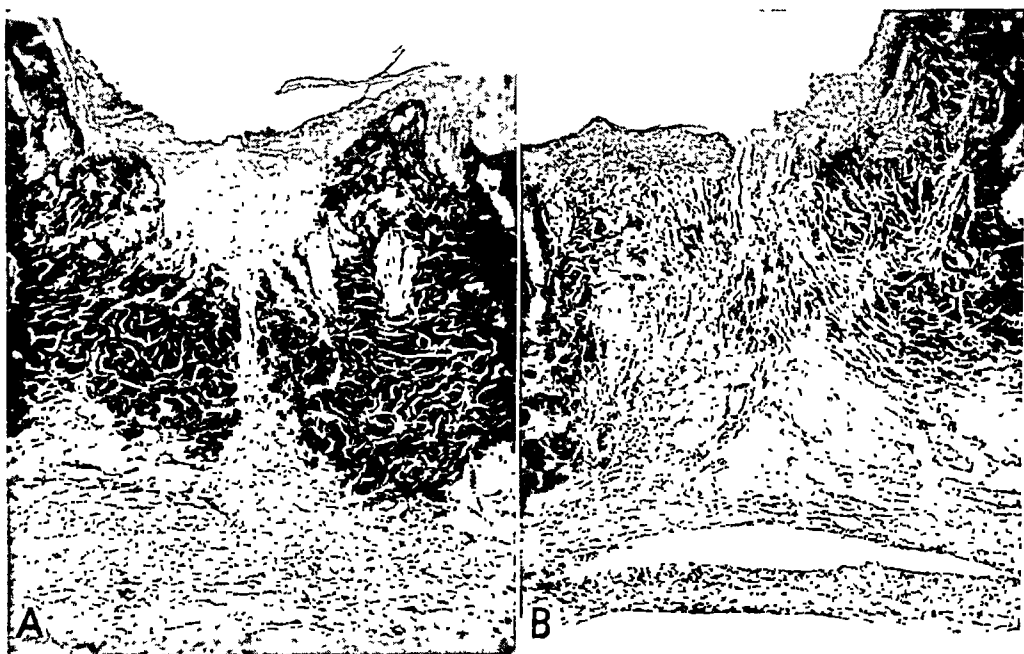


Fig. 1 (rat 10).—Photomicrographs of tissue taken from a wound treated twenty-four hours after cutting; the sections were taken eight days after cutting. *A* shows the treated part; *B*, the untreated part. Note the inflammatory exudate and lack of fibroblastic growth in *A*, and the inconspicuous scar in *B*. Hematoxylin and van Gieson stain. Zeiss apochr. 5, homal II; $\times 50$.

mechanism was not impaired in many cases, for the phagocytic cells seem to have cleared up the traumatic inflammatory exudate entirely, leaving the two edges of the cut close together, but separated by a histologic open space (fig. 2).

2. The atypical cells seen were in the form of fibroblastic giant cells. The chief difference from typical fibroblasts was in the size of the cells. There was usually no great distortion or abnormality of shape noted; the nuclei, though abnormally large, maintained for the most part the usual oval shape, though the nucleoli were more accentuated than in

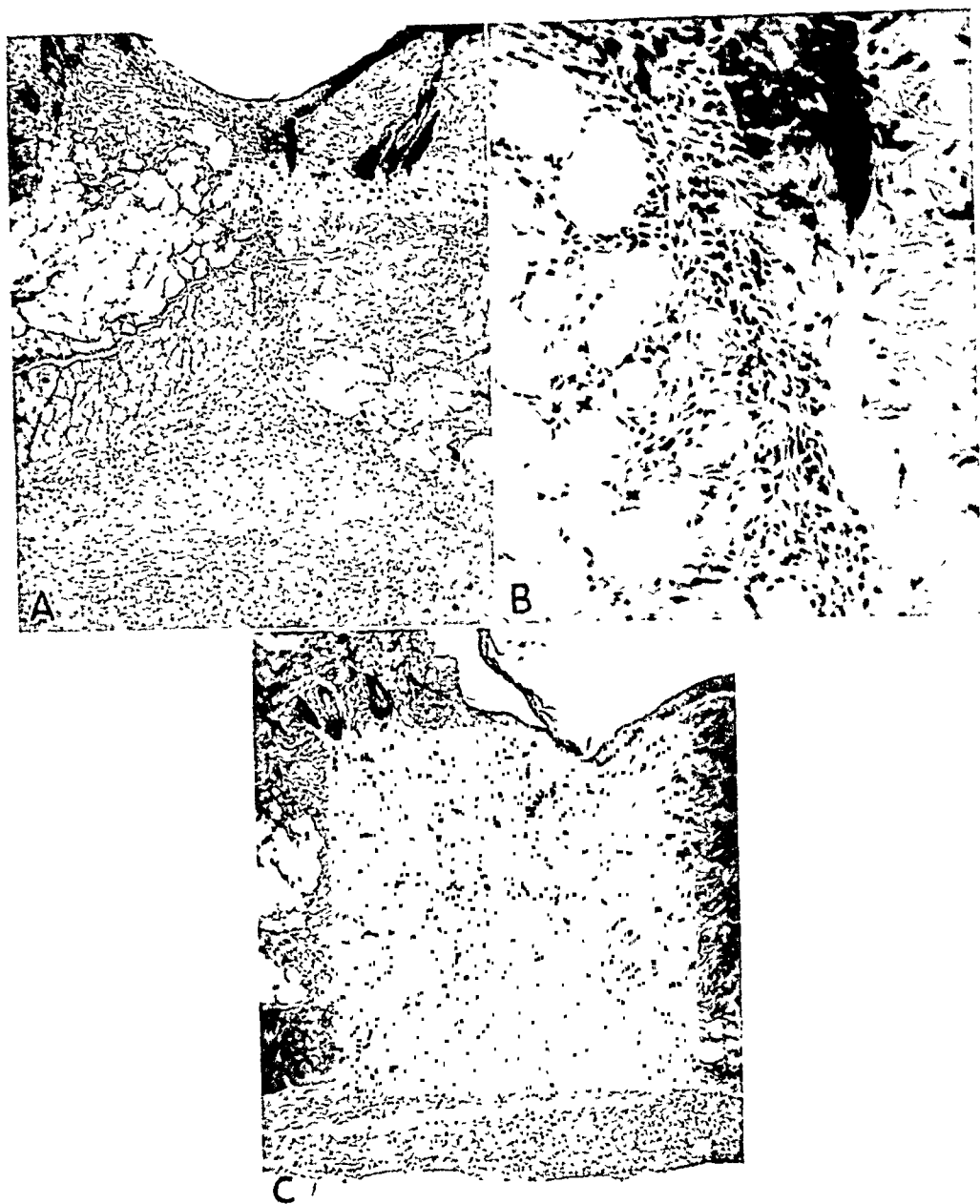


Fig. 2 (rat 3).—Photomicrographs of tissue from a wound irradiated immediately after cutting; the sections were taken seven days after cutting. *A* shows the treated part; *B*, detail of *A*; *C*, the untreated part. There is good approximation in *A*, with complete epithelial repair, but lack of fibroblastic growth, leaving a histologic space; also abundant unorganized inflammatory exudate in the deeper portion. Hematoxylin and eosin. *A* and *C*, Zeiss apochr. 5, homal II ($\times 50$); *B*, Zeiss apochr. 10, homal I; $\times 175$.

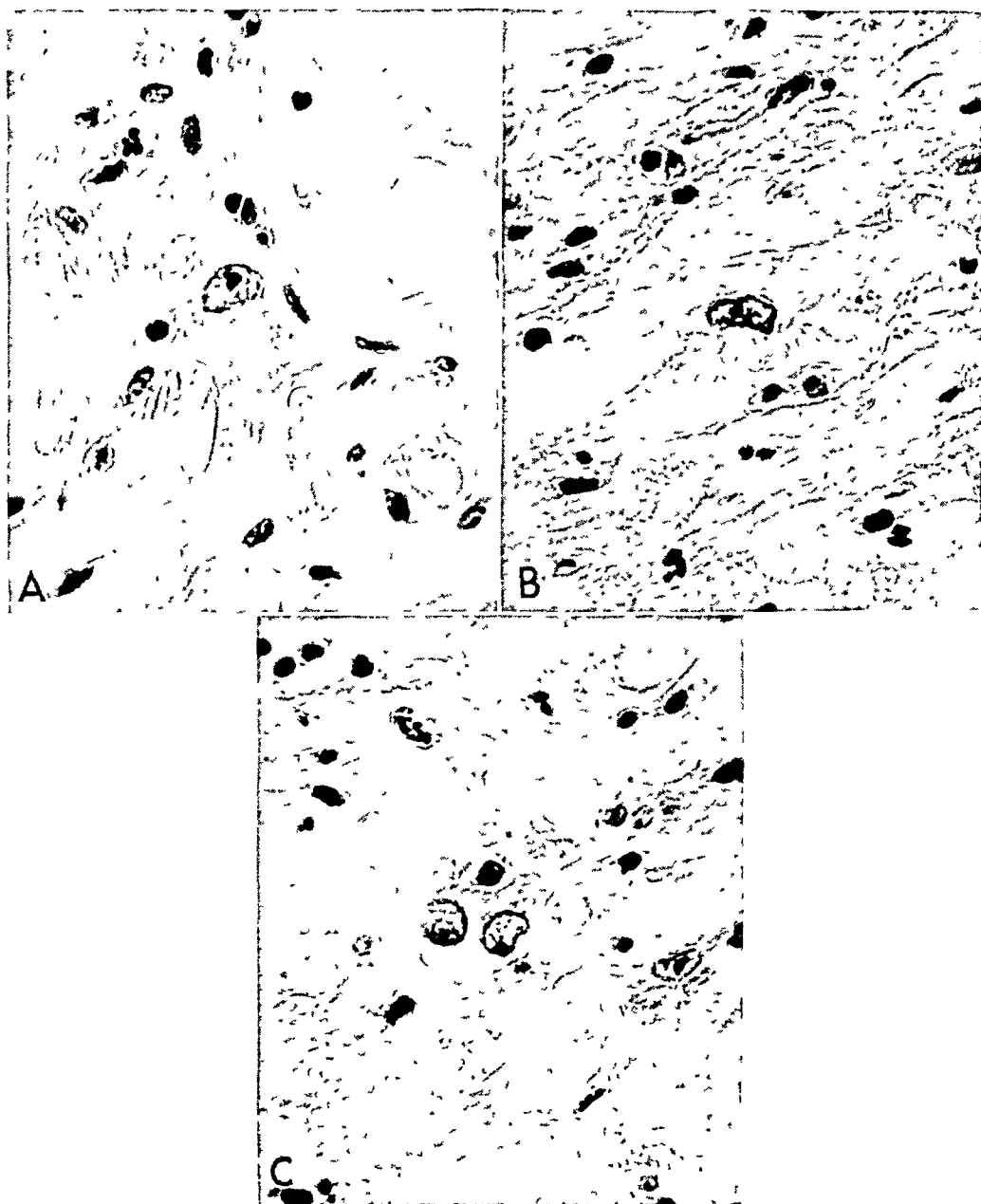


Fig. 3 (rat 16).—Photomicrographs of tissue from a wound exposed to irradiation forty-eight hours after incision. The sections were taken eight days after incision. In *A* a fibroblastic giant cell is seen in the treated part of the wound. In the surrounding tissues are inflammatory and connective tissue cells of usual size. In *B* is seen a fibroblastic giant cell with an indented nucleus; in *C*, a giant fibroblast with two nuclei. Iron hematoxylin stain. Zeiss apochr. 20, homal I; $\times 470$.

the control specimens (fig. 3 *A*): occasionally a nucleus was considerably indented (fig. 3 *B*), or there were two nuclei in one cell (fig. 3 *C*). This qualitative change in the repair process was the most frequent one seen, and was present even in several instances in which healing seemed as far advanced in the exposed part as in the control part of the wound.

3. The loose fibrin network seen in several cases was undoubtedly the remains of the original traumatic inflammatory exudate brought out by the injury to the tissue in cutting. It was noted formerly in our work, and its presence probably arose from a lack of proteolytic activity on the part of the cells in the region of the wound. This network was refractile, stained pink with eosin and yellow with van Gieson's stain, and seemed to be identical in all respects with that described by Maximow in his work with irradiated inflammatory tissue.

A quantitative analysis of these observations is of considerable interest. For convenience, the aforementioned groups of animals will be known as the "immediate," the twenty-four hour and the forty-eight hour group.

In the immediate group (total, twenty-nine animals), healing in the irradiated portions was retarded in thirteen. This delay was first noticeable three days after incision, and was present in all four animals killed six days after cutting. The examination of four seven day old wounds revealed delayed healing in the irradiated portions of two.

In the twenty-four hour group, the largest proportion of wounds with retarded healing resulted. Of twenty animals in this group, thirteen showed delayed healing in the treated parts. This retardation was first evident four days after incision, and was a constant observation at from five days to eight days, the extent of the experiment in this group.

In the forty-eight hour group, only five of seventeen animals showed positive results. In the rest there was no retardation of healing. No stage was found in the incisions at which a delay in healing was constant.

To sum up this portion of the results, delayed healing was present in thirty-one of sixty-six animals; the x-rays seemed most deleterious when administered twenty-four hours after incision, less so when roentgen treatment was applied immediately, and least deleterious in the forty-eight hour group. It may be said that in tabulating these results, only those differences which were absolutely clearcut were accepted as positive. In three animals a reversal of the usual effect was found; that is, there was an advance in healing in the treated portions over that found in the control parts. I am somewhat at a loss to explain this; since it occurred in such a small proportion of the total number of animals, I have laid it to technical error, a conclusion which I feel is fairly justified.

As mentioned previously, the formation of fibroblastic giant cells was the most frequent change noted. In forty-one of the sixty-six animals, these abnormal cells were found, being present in almost all cases in which a definite difference in healing could be detected between treated and untreated parts, and in several in which no such difference was noted. These cells appeared as early as two days after cutting (in two animals of the immediate group) and were present as late as nine days after cutting. Slight irregularities of fibroblasts were seen in some control tissues, but in no case were they as definite and striking as in the experimental portions. They were found in thirteen of the immediate group (total, twenty-nine), fifteen of the twenty-four hour group (total, twenty), and thirteen of the forty-eight hour group (total, seventeen). These proportions would seem to place this change as the most frequent and characteristic response to roentgen irradiation, though not the most important from a practical point of view, as it does not seem to affect the progress of healing.

The presence of a fibrin network is perhaps more difficult to evaluate quantitatively. In a wound which is not completely closed by sutures or clips, one would expect to find in all cases a certain amount of fibrinous exudate, usually more abundant in some parts of the wound than in others; the decision as to whether this is excessive must of necessity be arbitrary. For this reason I consider this phenomenon the least important of the three under discussion. For the sake of completeness, however, it might be well to make a brief statement as to quantitative results. I have eliminated for this purpose all animals killed four days or less after cutting, since a fairly large amount of fibrin network is certain to be present up to this time and even later. The phenomenon increases in significance, I believe, with an increase in the time after incision; under ordinary circumstances none should be present at seven days. Taking these facts into consideration, the network was present in only a small proportion of the animals: only fourteen of the sixty-six—four in the immediate group, seven in the twenty-four hour group and three in the forty-eight hour group.

The proportion of positive results previously mentioned may seem low until one considers that for the sake of completeness observations were begun in all three groups before any marked changes had taken place, and these early observations add to the proportion of negative results.

Here it may be noted also that in several instances the regenerated epithelium had completely covered the wound, while the underlying connective tissue showed no growth. The importance of this will be taken up later.

COMMENT

This subject may be regarded from two points of view: the first consideration is the treatment of the wounds, either with the purpose of acceleration of healing or with that of obtaining a better cosmetic effect; the second consideration is the postoperative irradiation of malignant tumors. Since the latter is by far the more important, attention has been devoted in this investigation entirely to that phase of the problem. For this reason the constant dose of 1,000 roentgens was chosen as approximating an average therapeutic dose. This appears high, but one must remember that when a dose of 500 roentgens is applied over a fairly large area, as in the treatment of carcinoma, the actual dose delivered, owing to back-scattering, may be as high as 700 roentgens. On the other hand, with the small areas used here (usually 1 by 3 cm.), the back-scattering is negligible, and the measured dose is for all practical purposes identical with the dose delivered to the tissues. Our dose is a little over the average one given in one sitting in the treatment of malignant new growths.

The results obtained here are practically identical with those of Maximow,³ who induced inflammation by the introduction of blocks of sterile pyroxylin (celloidin) under the skin. He administered about 12 Kienböck units at a sitting, with daily sittings ranging in number from one to fifteen. His paper does not give all the factors, but from those given I have calculated that the daily dosage was probably about 450 roentgens, given over a circular area 4 cm. in diameter. He found excessive fibrin, malformed fibroblasts and a lack of ability to form collagenous tissue in all cases, the changes differing only in degree according to the number of exposures. He found also that after complete healing the scars in experimental tissues were identical with control scars.

The mechanism of the delayed healing and of the formation of fibroblastic giant cells seems fairly clear in the light of modern radiobiology. It is generally agreed from work with tissue culture that cells in a process of mitotic division are most susceptible to the influence of x-rays; this is borne out by clinical and experimental observations. It is therefore natural that the fibroblasts, being in a most active state of proliferation, should show striking anomalies under the influence of an agent designed expressly to damage rapidly reproducing cells. One might expect to find a similar effect on the endothelium of the newly formed blood vessels, but such is not the case: A diligent search revealed only a normal capillary lining, without giant cells. The reason for this is not certain, but should probably be attributed to that obscure phenomenon, the biologic difference in susceptibility of different tissues to physical and chemical agents.

3. Maximow, A. A.: *J. Exper. Med.* **37**:319, 1923.

The relation of this anomalous fibroblastic formation to the rate of healing is not quite clear. It occurred in greatest proportion in the forty-eight hour group, in which the delayed healing was least frequent; it could therefore perhaps be regarded as evidence of slight cellular injury, as opposed to a more severe injury resulting in lack of regenerative activity and consequent sluggish healing.

The persistence of the fibrin network is also difficult to explain. Observation in general points toward the digestion of a fibrinous inflammatory exudate by the incoming phagocytic cells, though it sometimes takes place when relatively few of these are present. It is rather hard to conceive of an impairment of the function of incoming cells by localized irradiation lasting a comparatively short time (twenty-five minutes). The two most probable reasons for persistence of the fibrin network are, first, a change in the local p_H , caused by a perverted metabolism of the cells affected by roentgen rays, and, second, the lack of an enzyme supposedly secreted by the fibroblasts. Conclusive evidence in favor of either of these suppositions is lacking, so far as I have been able to ascertain. Von Gaza ⁴ stated that during the healing process the newly formed fibroblasts and capillary endothelial cells take a phagocytic part in the clearing up of débris, but he cited no experimental evidence as a basis for his statement. It is a well known fact, however, that in tissue cultures of fibroblasts, the culture medium becomes softened and digested in a short time. Santesson ⁵ reported a definite decrease in this softening following irradiation of cultures of chicken sarcoma. This would seem to indicate that there is a proteolytic enzyme secreted by such cells in culture, and further that this secretion is reduced by roentgen irradiation. The fact that x-rays, although causing destruction of cells, decrease the digestion of the medium, would lead one further to believe that this enzyme is not merely set free by the breaking down of dead cells, but is actually secreted by the living cells. It is recognized, of course, that such fragmentary evidence drawn from experiments with tissue cultures cannot be the basis of closely knit deduction applied to tissues in vivo; the facts are merely presented as being suggestive.

The question as to why the tissues appear most susceptible about twenty-four hours after injury is also a matter for considerable conjecture. Careful microscopic examination of our wound material does not lead to a satisfactory answer, but on the contrary merely convinces me that the problem is essentially a biologic one, not to be solved with present day histologic technic. A cursory review of the literature con-

4. von Gaza, W., in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1926, vol. 14, pt. 1, p. 1152.

5. Santesson, L.: *Upsala läkaref. förh.* **34**:591, 1928; abstr., *Zentralbl. f. d. ges. Radiol.* **6**:252, 1929.

cerning tissue cultures as influenced by irradiation, however, leads one to two definite conclusions: (1) A cell in, or about to undergo, mitosis is especially sensitive to the influence of roentgen rays; (2) therefore, the stage at which a tissue is most actively growing (hence contains the most mitotic figures) is the stage at which that tissue will be most susceptible. Opinions have varied as to the exact time when a cell is most sensitive. Markovits⁶ advanced the opinion that a cell in the equatorial plate stage is most easily destroyed. Love,⁷ in a series of experiments in which he used cultures of cells from the choroid and sclerotic of chick embryos, calculated that when a cell was within three hours of dividing (that is, when it was destined to divide at any time within the next three hours) its sensitivity to x-rays was constant; when such a period was over three hours, the sensitivity decreased. He believes that the reduction of mitoses in a culture exposed to roentgen rays is caused by an inhibition of the cells falling within the three hour stage.

Again we have evidence from experiments with tissue cultures which cannot be taken bodily and applied to naturally growing tissues. Still, when we link these facts to our knowledge in regard to malignant tumors and their susceptibility to x-rays, I think that we may safely deduce from the results obtained that the stage of most rapid cell growth in the healing of the experimental wounds occurred at a time not far from twenty-four hours after the wounds were made.

Another parallel may be drawn between experiments with tissue cultures and results obtained in the tissues themselves. When cells in tissue cultures are exposed to a dose of x-rays which injures the cells but does not cause actual death of the culture, the ultimate result is in most cases complete recovery, and after several days experimental and control cultures cannot be differentiated microscopically. Maximow⁸ found that scars in irradiated inflammatory tissue were identical with those in control inflammatory tissues, although, as previously related, x-rays exerted a striking influence on the earlier changes. Again, Pohle, Wright and I,¹⁰ working with rats, noted that although a single dose of 1,000 roentgens definitely delayed healing, the ultimate result was identical with that seen in unirradiated wounds, both grossly and microscopically.

A survey of the literature dealing specifically with the effect of roentgen irradiation on the healing of wounds reveals a surprising lack of attention to this important subject; indeed, no accurately controlled experimental work applying modern dosimetry has been reported, to my knowledge.

6. Markovits, J.: *Arch. f. exper. Zellforsch.* **6**:315, 1928.

7. Love, W. H.: *Arch. f. exper. Zellforsch.* **11**:435, 1931.

Haberland,⁸ in 1923, irradiated Thiersch skin grafts in nine dogs, and found a delay in healing. The difference between the control and experimental grafts was found to have disappeared after ten days. The dose used is given as from one-third to two-thirds unit skin dose, but since no qualifying data are given, it is impossible to calculate this accurately in roentgens. The highest dose was probably, however, not more than 400 roentgens. No histologic observations are given.

In 1928, Frey⁹ undertook a series of experiments designed to ascertain the vascular reaction to exposure to roentgen rays. He drew certain conclusions as to the healing of wounds after irradiation which I feel are not valid, as he did not work with wounds, reported no histologic observations and assumed that the reaction of the tissues was entirely vascular.

In the same year, Cazzamali¹⁰ injected trypan blue into the tissues a few days before and immediately following the production of wounds. He concluded that exposure to x-rays caused an earlier mobilization of the reticulo-endothelial elements in the healing process. The original article was not available to me, and the details of method and dosage are not given in the abstract.

Schürch and Tschudi¹¹ found that wounds treated with roentgen rays healed more quickly when they were made by means of electric cautery than with an ordinary scalpel. No histologic results were recorded.

F. Freund¹² and Fukase,¹³ working together, applied 400 roentgens to freshly made wounds in the skin of rabbits and noted acceleration of healing, with a decrease in the inflammatory exudate, particularly in the leukocytes. Recent work by Buhtz¹⁴ indicates, however, that Freund and Fukase did not begin their observations soon enough after incision; in the first few hours there is an increased outpouring of leukocytes, which disappear rapidly, giving the impression later of a decrease in exudate.

Businco and Cardia¹⁵ used dogs, four in all, and made two wounds on the back of each. They used one wound for the experiment and the other, on the opposite side of the vertebral column, as a control. The dose was one-third erythema dose, spark gap 30 cm., filter 3 mm. aluminum (about 150 roentgens), given to two dogs at a single sitting,

8. Haberland, H. F. O.: *Klin. Wchnschr.* **2**:353, 1923.

9. Frey, S.: *Beitr. z. klin. Chir.* **144**:574, 1928; *Deutsche Ztschr. f. Chir.* **212**:324, 1928.

10. Cazzamali, P.: *Abstr., Clin. chir.* **4**:781, 1928.

11. Schürch, O., and Tschudi, E.: *Strahlentherapie* **32**:143, 1929.

12. Freund, F.: *Strahlentherapie* **33**:375, 1929.

13. Fukase, S.: *Virchows Arch. f. path. Anat.* **273**:794, 1929.

14. Buhtz, H.: *Frankfurt. Ztschr. f. Path.* **44**:57, 1932.

15. Businco, O., and Cardia, A.: *Riv. di radiol. e fis. med.* **2**:378, 1930.

twenty-four hours after cutting, and to the other two dogs in two sittings (after twelve hours and three days, and after twenty-four hours and four days). This resulted in a stimulation and acceleration of healing. Histologic results were promised for a later communication, but this I have not been able to find.

In a series of experiments on rabbits, Podestá¹⁶ found that the irradiation of wounds, with either x-rays or radium, caused a delay in healing up to complete lack of closure, according to the dosage. His dose of roentgen rays varied "from a simple epilation dose to one causing a severe radiodermatitis, always with a heavy filter." There resulted necrosis in the depths of all wounds, and he concluded that if a heavy dose of either radium or x-rays is given over a fresh wound, necrotic tissue must be allowed to slough out before healing can be expected.

D'Istria and di Bello¹⁷ carried out an investigation, using various sorts of radiation on wounds. Their method consisted in stripping the skin from measured areas on the backs of animals and noting the progress of healing by daily measuring the unhealed areas. They reported an acceleration of healing by the use of doses ranging from 0.625 to 10 Holzkecht units (from 63 to 1,000 roentgens). Especial interest attaches to the fact that in this range, the smaller the dose used, the greater was the acceleration obtained. No histologic results were reported.

Thus, in spite of somewhat conflicting evidence, it appears from the various experimental investigations available that a small dose stimulates the healing process, whereas a larger one, approximating those used in the treatment of malignant tumors, causes a delay.

Clinical notes on this subject are not uniform as to the conclusions drawn, but in general bear out the experimental evidence. Vogt,¹⁸ in 1922, stated that preoperative irradiation caused no impairment of cicatrization. This is in accord with the observations of Pohle, Wright and myself.

In 1924, Schück¹⁹ reported briefly a series of cases in which he had treated various inflammatory conditions, such as pneumonia, with roentgen rays, with some apparent success. Heidenhain and Fried,²⁰ in the same year, reported a rather similar series of cases, with like results. No dosage is given in either communication. Halberstaedter and Simons (1926)²¹ stated that in their experience roentgen irradiation

16. Podestá, V.: *Riv. di radiol. e fis. med.* **2**:446, 1930.

17. d'Istria, A., and di Bello, F.: *Actinoterapia* **9**:95, 1930.

18. Vogt, E.: *Med. Klin.* **18**:1491, 1922.

19. Schück, F.: *Zentralbl. f. Chir.* **51**:1397, 1924.

20. Heidenhain, L., and Fried, C.: *Klin. Wchnschr.* **3**:1121, 1924.

21. Halberstaedter, L., and Simons, A.: *Acta radiol.* **5**:501, 1926.

tion caused delayed healing, though the ultimate scar tended to be smoother and more satisfactory from a cosmetic point of view. They noted also in one patient that after excision a malignant tumor recurred in the nonirradiated half of a wound but not in the irradiated half.

L. Freund²² observed that when keloids, lupus vulgaris and similar lesions were removed surgically, treatment of the incision with unfiltered roentgen rays (dose about 6 to 7 Holzknecht units, or approximately 700 roentgens) assured a soft inconspicuous scar. His communication was brief, and no time intervals were mentioned. Bab²³ reported a similar experience.

Jüngling²⁴ reported observations concerning preoperative irradiation and postoperative radium treatment of carcinomas. After doses of from 720 to 900 roentgens, given in from four to five sittings, he noted a slight increase in the difficulty of operation in some cases on account of fibrosis, but no increase in many cases. Following radium implantation, immediately after operation, the only complications noted by him were small areas of necrosis in the wound and a slight serous discharge persisting over a moderate period. He stated that skin grafts took well in such cases. No histologic observations were reported.

Huwer,²⁵ in a short communication, recently discussed the giant cells found following irradiation of carcinoma of the uterine cervix. He stated that some of these are derived from connective tissue. It is evident, however, from his illustrations that he was dealing with foreign body giant cells, probably brought out by the presence of necrotic cancer tissue, and not with the fibroblastic giant cells under discussion here.

Dr. Bunting²⁶ has seen giant fibroblasts in x-ray burns submitted to him for histologic examination.

I noted fibroblastic giant cells in two cases coming to my attention. In the first patient, a woman treated with radium and high voltage roentgen therapy for carcinoma of the uterine cervix, an ulceration of the intestine occurred; in the granulation tissue of the ulcer malformed fibroblasts were present, resembling closely those seen in experimentally irradiated wounds.

The second case was that of a man with carcinoma of the bladder. Electric fulguration was performed, causing an intense inflammatory reaction, and radium emanation seeds were implanted. The patient died about a month later, and in the inflammatory tissue taken post mortem could be seen the same phenomenon as in the first case—fibroblastic giant cells.

22. Freund, L.: *Deutsche Ztschr. f. Chir.* **222**:416, 1930.

23. Bab, M.: *Deutsche med. Wchnschr.* **57**:319, 1931.

24. Jüngling, O.: *Strahlentherapie* **44**:125, 1932.

25. Huwer, G.: *Zentralbl. f. Gynäk.* **54**:103, 1933.

26. Bunting, C. H.: Personal communication to the author.

The apparent contradictions in regard to the influence of roentgen irradiation on the healing of wounds arise, I believe, from two sources. First, the dose and method of application appear to be of great importance, the smaller doses having rather a stimulating effect, or at least causing no retardation, while a higher dosage comparable to that used in treating malignant tumors has a definite inhibitory influence on the repair process. Again the time interval is important, as discussed elsewhere.

Second, in investigations not including histologic examination a deceptive factor is introduced in the greater susceptibility of connective tissue as compared with that of epithelium. As previously mentioned, in our series of experimental wounds in the skin, several cases were noted in which the epithelium had entirely covered the wound, while the underlying connective tissue showed an almost entire lack of growth. Observed grossly, this would appear to be a perfectly healed wound, and might thus give rise to erroneous conclusions.

SUMMARY AND CONCLUSIONS

The results of an experimental investigation of the effect of roentgen rays on the healing of wounds are presented, with a brief review of the experimental and clinical literature on the subject.

The early histologic features found in such irradiated wound tissue are: (1) sluggishness of fibroblastic growth, (2) the presence of anomalous giant fibroblasts and (3) the persistence of a fibrin network for a varying period.

The first of these is considered to be most important from a practical point of view, and is most consistently seen when irradiation follows incision by approximately twenty-four hours. The second is the most constant characteristic, and since it has been noted also in human tissues subjected to roentgen and radium treatment, I think that its presence in inflammatory tissue is highly suggestive of a reaction to roentgen rays.

It is obviously improper to carry the results of animal experimental work bodily and in detail over into clinical practice; such an investigation can be seen in its true light only when thoroughly checked by clinical observation. Nevertheless, I think that enough evidence has accumulated to warrant the statement that roentgen irradiation in doses ordinarily used for the treatment of malignant tumors, administered within forty-eight hours after incision, may definitely retard healing but has no bad effect as far as ultimate results are concerned.

NOTE.—In the conversion of other units to roentgens, I have used the tables of T. C. Neeff (*Strahlentherapie* **33**:169, 1929).

CALCIFICATION OF THE SKIN IN DIABETES MELLITUS

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AND

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During the past few years abnormal calcification has attracted much attention among pathologists, clinicians and chemists. As far as we know, calcification never occurs in normal tissue, except in the formation of bone and in conditions spoken of as metastatic calcification. Any focus of dead or degenerated tissue that cannot be absorbed will probably become infiltrated with lime salts. Bearing these facts in mind, one is not surprised to find deposits of calcium in any organ of the body. Often the infiltrated tissue is dead, as in infarcts, caseous foci and inspissated collections of pus. Deposits of calcium may be found in inactive tissues, such as scar tissue, elastic tissue and ganglion cells of the brain which have become degenerated or necrotic. The scalp, muscle, myocardium, cardiac valves, arteries, veins, pleura, umbilicus, glands of internal secretion and prepuce have been found to be the site of deposits of calcium. Wiedman and Shaffer¹ reported a case in which calcium was distributed not only in the epidermis, but also widely throughout the corium, involving sweat glands and ducts, pacinian corpuscles and nerve trunks, as well as fibrous tissue of the corium.

Two forms of pathologic calcification are recognized. First, it occurs as a precipitation of calcium in secretions and excretions. This includes concretions in general, such as urinary and biliary calculi. Here we may explain the calcification by recognizable alterations in the composition of the secretion which leads to chemical precipitation. The second form is the type in which deposits of calcium salts are found in the tissues themselves, and is said by Bauer, Marble and Bennett² to be a rare condition affecting chiefly children. Langmead,³ Versé,⁴ Tisdall and Erb,⁵ Morse⁶ and Duret⁷ reported cases occurring in children. Duret

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1. Wiedman, F. D., and Shaffer, L. W.: *Arch. Dermat. & Syph.* **14**:503, 1926.

2. Bauer, W.; Marble, A., and Bennett, G. A.: *Am. J. M. Sc.* **182**:237, 1931.

3. Langmead, F. S.: *Arch. Pediat.* **40**:112, 1923.

4. Versé, M.: *Beitr. z. path. Anat. u. z. allg. Path.* **53**:212, 1912.

5. Tisdall, F. F., and Erb, I. H.: *Am. J. Dis. Child.* **27**:28, 1924.

6. Morse, J. L.: *Am. J. Dis. Child.* **22**:412, 1921.

7. Duret, cited by Bauer and co-workers.²

noted occurrence of the condition in brother and sister. This type cannot be explained by a single factor or etiology. It is evident that several factors, both local and general, may be contributory to such conditions. Certain forms of tissue calcification are well recognized and are to be distinguished from the type which we are reporting.

Myositis ossificans or intramuscular and intermuscular formation of bone is probably the most common.⁸ Under various pathologic conditions, bone is developed in the connective tissue in and between muscles. The formation of bone may begin in isolated muscles subjected to a single or repeated trauma or influenced by chronic inflammation in adjacent bones. As typical examples may be mentioned the formation of bone in the deltoid and pectoralis muscles, such as the so-called bayonettiers (bones from the impact of a gun), in the biceps of gymnasts and in the abductors of the upper thigh or of the vasti in horseback riders. Other forms of myositis ossificans, the etiology of which is obscure, are said to be more progressive and begin spontaneously, usually in early youth, first appearing in the muscles of the shoulder, the nape of the neck and the masseter muscles and then gradually spreading to the muscles of the back until all the muscles are involved. In some cases, malformations of the extremities, particularly microdactylia, have been observed. Probably the most widely accepted explanation is that there is a congenital, nonhereditary, reduced ability of differentiation of the connective tissue elements owing to a disturbance in the mesenchymal cells, and that as accompanying symptoms of the developmental inhibition there appear microdactylia and other malformations.

Metastatic calcification due to disease of the parathyroid glands is well known. Dawson and Struthers⁹ reported a case of generalized osteitis fibrosa with tumor of the parathyroid gland (adenoma) and metastatic calcification. The calcification occurred in all organs and tissues of the body. Barr¹⁰ stated that metastatic calcification has been observed several times in cases of hyperparathyroidism in which tumors of the parathyroid gland and osteitis fibrosa cystica have been associated. Collip, Clark and Scott¹¹ found that hypercalcemia may result from the administration of parathyroid hormone. Hubbard and Wentworth¹² observed metastatic calcification and hypercalcemia in a man with hyperplasia of the parathyroid gland. Hueper¹³ found that dogs given injections of parathyroid hormone show deposits of calcium in the thyroid.

8. Kaufman, Edward: *Pathology for Students and Practitioners*, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 3, p. 2051.

9. Dawson, J. W., and Struthers, J. W.: *Edinburgh M. J.* **30**:421, 1923.

10. Barr, D. P.: *Physiol. Rev.* **12**:593, 1932.

11. Collip, J. B.; Clark, E. P., and Scott, J. W.: *J. Biol. Chem.* **63**:439, 1925.

12. Hubbard and Wentworth: *Proc. Soc. Exper. Med.* **18**:307, 1921.

13. Hueper, Wilhelm: *Arch. Path.* **3**:14, 1927.

lungs, cardiac muscle, stomach—mostly in the fundus—duodenum and kidneys. Massive doses of viosterol have produced metastatic calcification.¹⁴

Rabl¹⁵ suggested the theory that the metastatic calcification sometimes seen without lesions of the bone, as in the so-called calcium gout, may depend on renal lesions with decreased elimination of phosphoric acid. The retained phosphoric acid is buffered by calcium withdrawn from the bones, so that the blood contains an abnormally high content of calcium. Whenever the p_H of the blood is raised, as by the taking of food containing an abundance of bases, the excess calcium is deposited in the tissues. Wildbolz¹⁶ Licharoff¹⁷ and Lewandowsky¹⁸ all agree that some forms of pathologic calcification are a disturbance of organic metabolism similar in character to gout, except that calcium salts are deposited instead of urates.

Durham¹⁹ reported a case with extensive subcutaneous, periarticular and vascular calcification associated with chronic nephritis (small, granular kidney) in which the serum calcium was slightly below normal. The calcification here also involved veins, arteries, the mitral valve, the myocardium and ulcers of the leg.

Disorders of uric acid, fat or cholesterol metabolism may be closely related to some forms of abnormal calcification, but the relationship is not constant. The case of Bauer, Marble and Bennett² did not show an appreciable increase in uric acid, fatty acids or cholesterol.

Much attention has been given to the presence of iron in calcified tissues. Sprunt,²⁰ and later, Bennett²¹ described cases of calcium and iron incrustation of the spleen. Both cases showed a predominance of iron and the presence of iron without calcium in some areas. Watts²² demonstrated the association of these two substances in the choroid plexus and concluded that certain features suggested strongly that calcification follows thrombosis of the vascular supply to the plexus. Kockel²³ and Bittrolff²⁴ reported cases of calcium and iron incrustation of elastic

14. Hükel, R., and Wenzel, H.: *Arch. Exper. Path. & Pharmacol.* **141**:292, 1929. Smith, M. L., and Elvove, E.: *Pub. Health Rep.* **44**:1245, 1929. Shohl, A. T.; Goldblatt, H., and Brown, H. B.: *J. Clin. Investigation* **8**:505, 1930.

15. Rabl: *Klin. Wchnschr.* **2**:202, 1923; *Virchows Arch. f. path. Anat.* **245**:542, 1923.

16. Wildbolz: *Arch. f. Dermat. u. Syph.* **70**:435, 1904.

17. Licharoff, cited by Pospelow.³⁰

18. Lewandowsky: *Virchows Arch. f. path. Anat.* **181**:179, 1905.

19. Durham, R. H.: *Ann. Clin. Med.* **5**:679, 1926-1927.

20. Sprunt, T. P.: *J. Exper. Med.* **14**:59, 1911.

21. Bennett, G. A.: *Arch. Path.* **7**:71, 1929.

22. Watts, J.: *Arch. Surg.* **15**:89, 1927.

23. Kockel: *Deutsches Arch. f. klin. Med.* **64**:332, 1899.

24. Bittrolff: *Beitr. z. path. Anat. u. z. allg. Path.* **49**:213, 1910.

fibers in lungs which were the seat of chronic passive congestion. The lesions were in the walls of small blood vessels and in the elastic tissue of the alveolar walls. Ehrlich²⁵ noted several instances of simultaneous calcium and iron incrustation of elastic fibers in scars of splenic infarction, in intestinal polypi and in the alveolar walls of the lungs. He concluded that elastic fibers in the neighborhood of hemorrhage have a special tendency to absorb iron and that such fibers may secondarily become calcified. Rona²⁶ and Hektoen²⁷ mentioned the finding of calcium and iron containing elastic fibers in giant cells in various inflammatory processes. Gierke²⁸ called attention to the physiologic association of calcium and iron in the fetus, in which the entire skeleton as far as it has been calcified contains iron, with an excess in the parts of active ossification. There is a considerable amount of controversy as to whether the iron or the calcium is deposited first. Some investigators claim that iron is deposited first and acts as a mordant for the calcium.

The formation of calcium soap is an important step in the process of pathologic calcification, but it is not essential. Wells²⁹ found doubtful traces of calcium soap in calcifying matter and small amounts of other soaps of fatty acids. Calcium soap implanted in tissues does not become transformed into calcium phosphate and carbonate, but is chiefly absorbed and removed. Wells therefore feels that chemical precipitation in the tissues is not responsible for the calcification, but that the latter depends on a physicochemical factor and variation in the concentration of carbon dioxide.

Versé,¹ in referring to several cases of generalized calcium deposits, called attention to the early changes in the intercellular substance of connective tissue. Pospelow³⁰ mentioned the affinity between elastic fibers and calcium salts, and expressed the belief that the deposit can probably occur in normal elastic tissue. He considered that calcium may be deposited in abnormal locations, either because the blood is saturated with calcium or because the solubility of calcium in plasma is changed, even though the blood calcium is not above normal.

Bauer, Marble and Bennett² concluded that the basis of the disorder lies in an abnormality of calcium and phosphorus metabolism. An increased retention of calcium and phosphorus may be the result of a local cellular condition as yet undetermined. In their case the studies of calcium and phosphorus balance indicated a marked tendency to retain

25. Ehrlich, S.: *Centralbl. f. allg. Path. u. path. Anat.* **17**:177, 1906.

26. Rona: *Beitr. z. path. Anat. u. z. allg. Path.* **27**:349, 1900.

27. Hektoen: *J. M. Research* **7**:159, 1902.

28. Gierke: *Virchows Arch. f. path. Anat.* **167**:318, 1902.

29. Wells, H. G.: *Chemical Pathology*, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 494.

30. Pospelow, W. A.: *Arch. f. Dermat. u. Syph.* **140**:75, 1922.

the absorbed calcium and phosphorus in spite of the normal blood calcium and phosphorus values. This was more marked for calcium than for phosphorus.

REPORT OF CASES

CASE 1.—An obese white woman, aged 66, was admitted to the New England Deaconess Hospital under the care of Dr. Elliott P. Joslin on May 15, 1932, with severe infection and gangrene of her left foot. She had had diabetes since 1918, and had received insulin therapy for the past three years. In August, 1929, she had a slight shock, involving the left arm and leg. This improved after ten days, but left some weakness which persisted. Three months before admission she noticed a festered area on the bottom of her foot. The condition improved with rest, but activity caused a discharge of a small quantity of pus. The infection



Fig. 1 (case 1).—Skin from the leg, showing deposits of calcium and the formation of bone in the subcutaneous tissue; decalcified; reduced from $\times 20$.

was drained one week before admission by incisions on the plantar and dorsal aspects of the foot. There was a foul odor and a discharge of pus and gas through the plantar region. The circulation was fair except for the absence of pulsation in the dorsalis pedis.

On admission the temperature was 102 F.; the pulse rate, 110, and respiration, 23. On May 18, under spinal anesthesia, the left leg was amputated just above the knee. The postoperative course was good.

The urinary sugar was 0.2 per cent on admission. The amount of sugar gradually increased, until on the fifth day it was 4.4 per cent. The following five days the amount of sugar steadily decreased to 0 and remained so until the patient was discharged from the hospital. The Wassermann test was negative. The blood nonprotein nitrogen varied from 30 to 108 mg. per hundred cubic centimeters; the blood sugar, from 0.19 to 0.74. The carbon dioxide of the blood was 40 per

cent. Analysis of the blood on May 16, 1933 (one year later) showed: sugar, 0.24 per cent; calcium, 10 mg. per hundred cubic centimeters; phosphorus, 3.1 mg. and cholesterol, 291 mg.

The specimen consisted of a left leg amputated just above the knee. It weighed 5,800 Gm. There were two fairly recent surgical incisions, one 2 cm. long, located on the dorsum of the foot between the third and fourth metatarsals; the second, 6 cm. long, on the plantar surface in the center of the ball of the foot. From each could be expressed foul-smelling, grayish-yellow, moderately thick pus. The necrosis extended through the soft tissues and apparently involved the bones of the foot. The posterior tibial artery showed medial and intimal sclerosis with calcification. The anterior tibial artery was similar, except that the lumen was apparently occluded in its distal portion by atheromatous plaques. The nerves

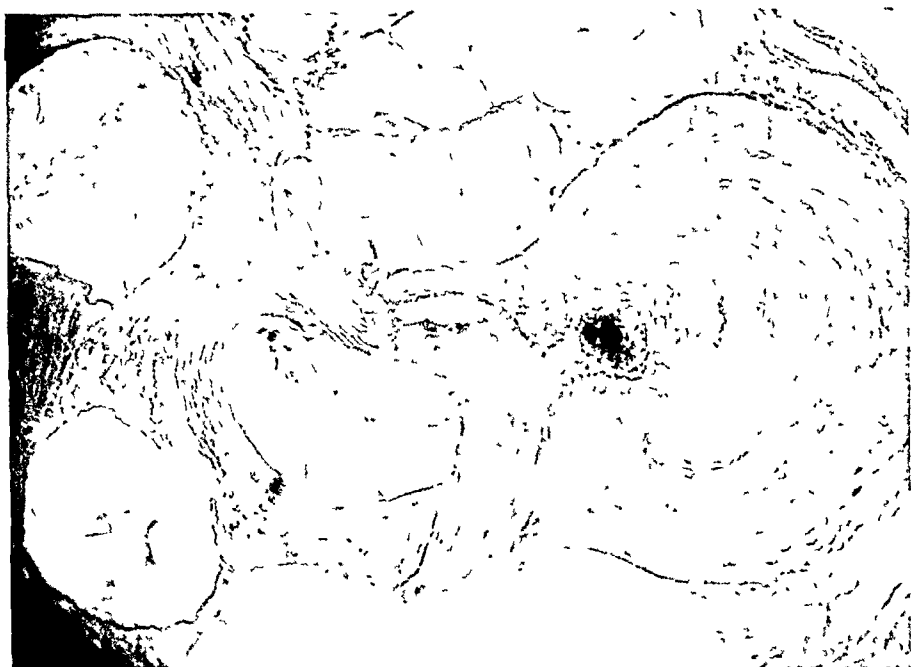


Fig. 2 (case 1).—Skin from the left leg showing bone with marrow spaces; decalcified; reduced from $\times 138$.

and veins were not remarkable. In the subcutaneous tissue of the leg could be felt many small spicules of calcification. A section of skin and tissue from the foot showed an extensive infiltration of polymorphonuclear leukocytes with necrosis and gangrene. The lumens of the anterior and posterior tibial arteries were almost occluded by intimal plaques. There were some edema, a small amount of fat, calcium and cholesterol, and slight infiltration of the intima with lymphocytes and endothelial cells. The media was greatly thickened and contained a large amount of calcium and a few spicules of bone. There were also proliferation of connective tissue and profuse infiltration of lymphocytes and endothelial cells. The adventitia was not remarkable.

The epidermis of a section of skin from the leg was not remarkable. Deep in the corium and in the subcutaneous tissue could be seen spicules of bone with fatty marrow (figs. 1 and 2). There was apparently no inflammatory reaction

or degeneration of the tissues other than hyalinization and calcification of the elastic fibers. Some of the small veins showed hyalinization and calcification of the media (fig. 3).

The roentgen examination, by Dr. I. K. Bogan, showed numerous, irregularly linear, calcium shadows in the soft tissues anterior to the middle portion of the left tibia. Smaller rounded shadows were seen throughout the soft parts of the leg to within a distance of 2 inches (5 cm.) above the ankle joint. These had about the density of plaques seen in arteriosclerotic vessels, and lay in the subcutaneous tissues. The arteries of the leg showed calcification, 3+. There was calcinosis (fig. 4).

CASE 2.—A white woman, aged 66, was admitted for the first time to the New England Deaconess Hospital to the service of Dr. Elliott P. Joslin on July



Fig. 3 (case 1).—Skin from the left leg. Vein showing calcification of the media; decalcified; reduced from $\times 150$.

10, 1930, on account of diabetes mellitus and multiple and chronic infections of the right leg.

She had had diabetes since 1927. In February, 1930, she had an infection of the great toe of the right foot, and later an infection and a discharge from the fifth toe on the same foot; four weeks afterward severe pain developed in the calf of the right leg. About July 1, 1930, an ulcer developed on the calf of this leg.

On entrance, the right foot was edematous and red, and there was an ulcerated area about 4 cm. in diameter on the lateral aspect of the lower portion of the right leg. The blood pressure was 190 systolic and 100 diastolic. Culture from the ulcer showed *Staphylococcus albus*. The urinary sugar was 8 per cent on admission, but was reduced to 0 during the first five days; the blood sugar was 0.26 per cent on admission and 0.13 per cent when the patient was discharged.

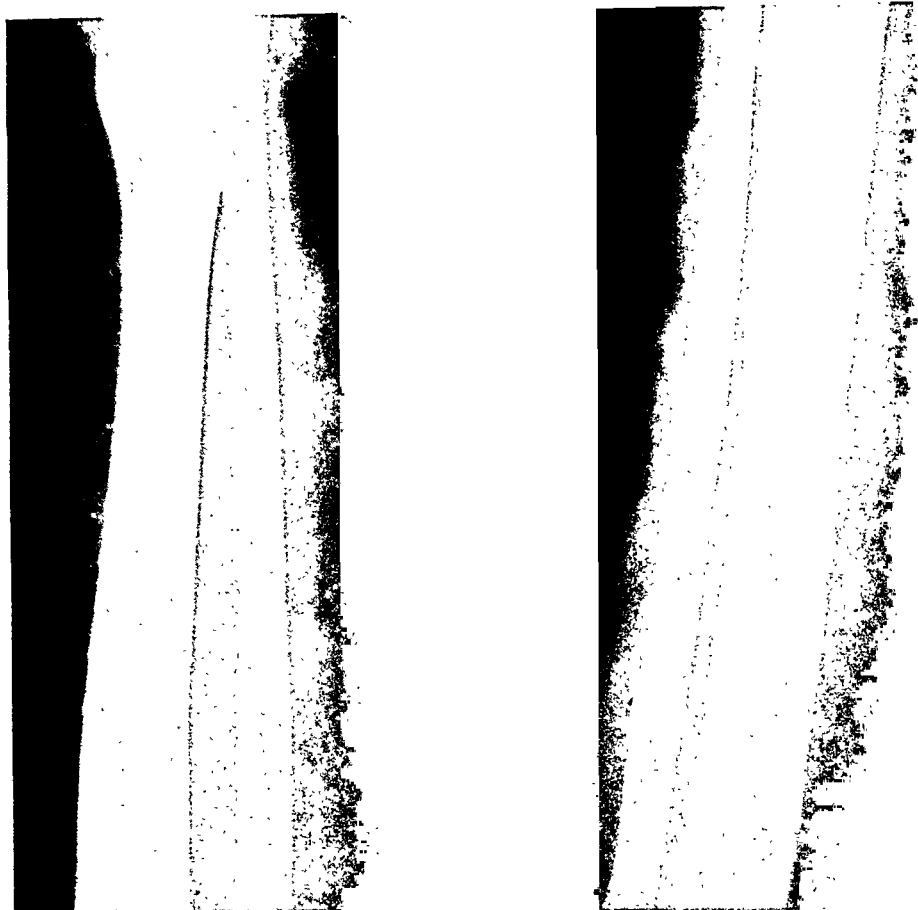


Fig. 4 (case 1).—Roentgenogram of the left leg showing calcification of the skin. Reduced.

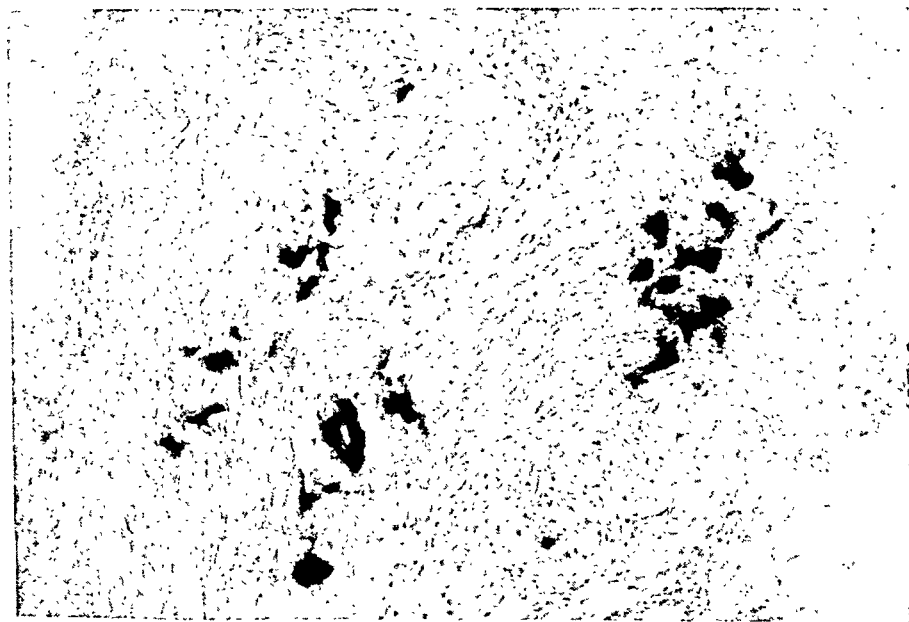


Fig. 5 (case 2).—Skin of the left leg, showing calcification; reduced from $\times 225$.

The dosage of insulin varied from 5 to 15 units daily. The ulcer healed slowly. The fifth toe on the right foot was amputated on July 30. The patient was discharged on October 2, improved.

The specimen consisted of the fifth toe amputated at the level of the metatarsal phalangeal joint. The subcutaneous tissues were soft. The microscopic diagnosis was chronic osteomyelitis.

The patient was admitted the second time on May 11, 1931, on account of superficial ulceration of the left foot. Slight glycosuria was present on admission, but disappeared following the use of 5 units of insulin daily for a week; no further insulin was necessary. The ulcer healed slowly.

The patient was admitted the third time on Dec. 14, 1931, on account of an ulcer on the left foot and 4 per cent glycosuria. The glycosuria disappeared abruptly on the administration of 10 units of insulin. On December 23, the lower portion of the left leg was amputated. The patient was discharged improved.

The specimen consisted of the left leg amputated at about the midcalf. It weighed 1,270 Gm. The small toe was black and gangrenous on the superior and medial surfaces and the distal end. A section from the small toe was black. The posterior tibial artery was hard and contained a considerable amount of calcium. The lumen was occluded to a diameter of 1 mm. The anterior tibial artery was wirelike and contained a considerable amount of calcium. About 2 cm. below the point of amputation, the lumen was about 2 mm. in diameter. The microscopic diagnosis was: gangrene; arteriosclerosis, intimal and medial type; arterial thrombosis with organization and canalization, and slight chronic osteomyelitis.

The patient was admitted the fourth time on Aug. 10, 1932, with gangrene and infection of the right foot. The lower portion of the right leg was amputated on August 11. The patient made an uncomplicated recovery and was discharged improved.

The specimen consisted of the right leg which had been amputated at the midcalf. The weight was 1,190 Gm. The small toe had previously been removed and a well healed surgical scar remained. The skin of the adjacent toe was dry and wrinkled. The third toe was black and gangrenous. The second toe was similar to the fourth. The great toe had a gangrenous area at the tip, involving the nail-bed and measuring 2 cm. in diameter. On the anterior surface of the leg in the distal third was a hard, black, ulcerated area 1 cm. in diameter. The anterior tibial artery was hard and tortuous and showed extensive intimal thickening and calcification. The lumen was patent. The posterior tibial artery was similar except that the lumen appeared to be completely occluded. The microscopic diagnosis was: gangrene; arteriosclerosis, intimal and medial type, and acute secondary osteomyelitis.

The patient was admitted the fifth time on Feb. 6, 1933, on account of gangrene of the amputation stump of the lower portion of the left leg. Amputation was done at the mid thigh on February 9. The urinary sugar on admission was 3 per cent and was soon reduced to 0. On February 16, the blood calcium was 10.1 mg. per hundred cubic centimeters; the cholesterol, 197 mg. The postoperative course was good. The patient was discharged on February 23, improved.

The specimen consisted of a portion of the left leg. The secondary amputation was made from the midcalf to the mid thigh. The distal end contained a hard, black, gangrenous area about 9 cm. in diameter, partially covered with a brown crust. At the distal end of the posterior tibial nerve was a small tumor mass 0.5 cm. in diameter, firm and white. The arteries were markedly sclerosed and calcified. On section of the knee joint, the articular cartilages showed erosions, marked overgrowth and calcification along the edges. One of the sections showed

extensive necrosis and gangrene with the deposition of small and large foci of calcification. In some of the sections deposits of calcium were found in areas in which there was no evidence of inflammation or degeneration other than hyalinization and calcification of the connective tissue. Some of the calcium appeared as small, basic-staining granules (about 1 micron in diameter) scattered rather diffusely throughout the corium and subcutaneous tissues. Other deposits were much larger and apparently represented a conglomeration of the small granules. The femoral and posterior tibial arteries contained large intimal plaques with an infiltration of endothelial cells and accumulation of some fat, cholesterol and calcium. The media was thickened and contained a considerable amount of calcium. The adventitia and veins were not remarkable. A diagnosis of gangrene, arteriosclerosis (chiefly medial) and slight calcification of the corium was made.

The roentgen report, by Dr. I. K. Bogan, on February 16, showed that the vessels of the left leg and of the thigh and upper portion of the right leg showed extensive calcification. A linear area of density was seen internally, opposite the right knee joint, which was compatible with the presence of calcium in the skin.

COMMENT

In the two cases presented the patients were women, each 66 years of age with a history of diabetes for fourteen and six years, respectively. The clinical course of each did not differ from that of diabetic patients who do not show deposits of calcium in the tissues. In both cases the blood chemistry was not remarkable for diabetic patients, and the calcium was within normal limits, as was the cholesterol in case 1. It was not possible to make additional studies.

There was no evidence of any abnormality of the parathyroid glands. The patients did not receive viosterol. If impaired circulation was a factor, it is surprising that this lesion has not been found in others of the many gangrenous legs examined in this laboratory. Evidence of significant renal lesions was lacking. It is possible, though unlikely, that the inflammatory process in the gangrenous foci may have influenced the deposition of calcium in case 2, yet, according to the roentgen report, there were deposits of calcium in the corium at least 15 cm. from the zone of inflammation. In case 1 the calcification was even farther from the focus of inflammation.

SUMMARY

Unexplained calcification of the subcutaneous tissues and corium was found in two elderly diabetic patients. The usual causes for metastatic calcification have been ruled out.

AN ANATOMIC MECHANISM IN THE PRODUCTION OF THE FLINT MURMUR

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In 1862, Flint¹ reported two cases of aortic insufficiency in which a presystolic blubbery murmur occurred in the mitral area. At autopsy an insufficiency of the aortic valves was established, but no lesions of the mitral valves were found to account for the well marked mitral presystolic murmur. In explanation, Flint suggested a floating up of the mitral leaflets with the filling of the left ventricle, and since in cases of considerable aortic insufficiency, the left ventricle is rapidly filled with regurgitant blood from the aorta as well as from the auricle, the distention of the ventricle might be such that the mitral curtains are brought into coaptation. When auricular contraction then takes place, the mitral direct current passing between these curtains throws them into vibration and gives rise to the characteristic blubbery murmur. Flint considered the physical condition in effect analogous to a contraction of the mitral orifice from an adhesion or an approximation and fixation of the curtains at their sides, such as in organic mitral stenosis gives rise to the mitral direct murmur of similar character.

Herrmann,² in reviewing the significant historical facts concerning the discovery and explanations of the Flint phenomenon, mentioned the original and various modified explanations of the mechanism as offered by Sanson,³ Phear,⁴ Gibson,⁵ Broadbent,⁶ Guiteras,⁷ Da Costa,⁸ Futch⁹ and Huffman.¹⁰ Herrmann pointed out that in experimental animals

From the Department of Pathology, the Long Island College of Medicine, the Hoagland Laboratory.

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8. Da Costa, J. C.: *Physical Diagnosis*, Philadelphia, W. B. Saunders Company, 1913, p. 310.
9. Futch, T. B.: *Outlines of Physical Diagnosis*, Baltimore, Students' Book Store, 1920, p. 63.
10. Huffman, O. V.: *M. Rec.* **93**:681, 1918.

lesions of the posterior cusps, especially extensive puncture wounds near the basal attachments, are most likely to produce the phenomenon. He also described the cases of two persons who presented the Flint phenomenon during life and who showed incompetency of the posterior aortic cusps at autopsy.

A review of the literature on the subject leaves the impression that knowledge of the mechanism still remains unsatisfactory and vague. The following two cases are presented, since in them a definite organic lesion, not involving primarily the mitral valve, seems to offer a definite and concrete explanation for the Flint murmur that was observed during the life of these two persons.

REPORT OF CASES

CASE 1.—A white man, aged 25, entered the Long Island College Hospital complaining of chills and fever and of pains in the legs. His past history for the most part was irrelevant. He had scarlet fever at the age of 4 years, and had never had rheumatic fever, tonsillitis, diphtheria, typhoid fever or pneumonia. He said that he had never had syphilis or gonorrhea. The present illness dated back about a month before admission, when he experienced sharp pains in his arms and legs. He continued to work until two weeks before admission, when he had a severe chill and fever. Several days before admission he became drowsy and nauseated. On admission he complained of headache, dizziness and pains in the extremities.

Examination showed a fairly well developed and nourished young man, apparently 25 years of age, lying in bed and in no respiratory distress. The lips and nails were cyanotic. Numerous petechiae were scattered over the neck, face and thorax. The apical impulse of the heart was seen and felt in the fifth interspace. The sounds were of good quality. Examination of the heart revealed only a pre-systolic blubbery murmur in the mitral area. No signs of aortic regurgitation were present on admission. The blood pressure was 110 systolic and 70 diastolic. Examination of the lungs revealed nothing of significance. The abdomen was soft and very full and had many petechial spots. The splenic and hepatic edges were not palpated. The Wassermann reaction was negative. A culture of the blood revealed 136 colonies of *Streptococcus viridans* per cubic centimeter. The urine showed a large quantity of albumin, numerous white blood cells and red blood cells and coarse granular casts. Two days after admission signs of aortic regurgitation suddenly developed, and the late diastolic murmur at the mitral areas was still present. The blood pressure was 120 systolic and 40 diastolic. The patient's condition gradually became worse, and he died nine days after admission.

Autopsy showed the following: The lungs were moderately congested. The liver was normal in size, weighing 1,650 Gm., and the lower edge was slightly rounded. On section, a moderate degree of passive congestion was noted. Examination of the gastro-intestinal tract revealed nothing of pathologic significance. The spleen was enlarged, weighing 500 Gm., and scattered over its surface several yellow infarcted areas were found. The kidneys were normal in size and shape and quite firm in consistency. Their capsules stripped with ease. Several small infarcted areas from 1 to 2 cm. in size were found in both kidneys. The pericardial sac contained 30 cc. of clear yellow fluid. There was no exudate on the epicardial or pericardial surfaces. The heart was normal in size and shape, weighing 300 Gm. The muscle of the left ventricle was firm in consistency. When this

chamber was opened the mitral leaflets were normal. They were not thickened, shortened or grown together. The chordae tendineae were not thickened or shortened. There was no stenosis of the ostium or insufficiency of the valve. On examination of the aortic valve a large vegetation 2 cm. in diameter was found suspended from the base of the posterior cusp, and a large perforated window of the cusp was also noted. A vegetation 1 cm in diameter was also found on the right anterior cusp. The cusps were not thickened, grown together or retracted; that is, no evidence of a previous endocarditis was found. The remaining cardiac valves were normal (fig. 1).



Fig. 1 (case 1).—The normal mitral leaflet is seen, and near its attachment the vegetations on the aortic valves are visible. The interference produced by these vegetations in the function of the anterior leaflet of the mitral valve is shown in figure 2.

CASE 2.—A white woman, aged 44, was admitted to the Long Island College Hospital complaining of swelling of the ankles, dyspnea, precordial pain and vomiting. The family history was irrelevant. She had rheumatism at 11 years of age and was sick for three months, recovering without complications so far as she knew. She had malaria at 16 years of age, whooping cough at 21 years, and pneumonia three times between the ages of 27 and 30 years, recovering from all without complications. She said that neither she nor any one of her several

husbands had ever had a venereal infection. The present illness began six months before admission; following a severe cold, she collapsed on the street complaining of severe dyspnea, palpitation and dizziness. After two months' rest in bed she recovered sufficiently to be able to swim and dance and felt entirely well. Two months later she experienced a similar attack and was admitted to a hospital where she remained for six weeks. During her hospitalization a roentgenogram was taken, and she was told that she had a pericardial effusion. A few days after discharge from the hospital a peritonsillar abscess developed which ruptured spontaneously. She then suffered a return of her previous symptoms and was admitted to the Long Island College Hospital with the complaints noted.

Examination showed a well developed and nourished woman. There was moderate cyanosis of the lips and nail-beds. The patient was orthopneic. Her pupils were slightly unequal but regular and reacted to light. The throat was moderately injected, and the tonsils were small and ragged and appeared infected. The veins of the neck were full when the patient was erect in bed. The apical impulse was localized in the sixth interspace in the anterior axillary line. The cardiac rhythm was completely irregular. A thrill was felt over the apex, apparently presystolic, although the time was uncertain. Systolic and diastolic murmurs were heard at the base. After a short course of quinidine therapy, the cardiac rate became regular, and at this time a late rumbling diastolic murmur was heard at the mitral area in addition to the to and fro murmurs at the base. The family physician also had reported hearing a presystolic murmur in the mitral area on certain occasions. The pulse was of the Corrigan type. The blood pressure was 140 systolic and 35 diastolic; the temperature 100 F.; the pulse rate, 90, and respiration, 23. The abdomen showed tenderness in the right upper quadrant. Breath sounds were vesicular throughout both lungs, except at the right base where many subcrepitant râles were heard. The blood count showed: red blood cells, 3,800,000; hemoglobin, 75 per cent; white cells, 10,500, and polymorphonuclears, 71 per cent. Urinalysis showed a specific gravity of 1.028 and a faint trace of albumin. There were no acid bodies or reducing substances, and the sediment did not contain formed elements. The Wassermann and Kahn reactions of the blood were 4 plus. In the electrocardiograph, the Q R S groups were slurred in all leads; the T waves were inverted in lead I, indicating ventricular myocardial disease. The blood culture was negative. Several days later the patient died of cardiac failure.

Autopsy disclosed the following: There were hemorrhagic infarcts in the lower lobes of both lungs. Emboli were present in the branches of both right and left pulmonary arteries. The liver showed fatty degeneration and moderate passive congestion. The kidneys showed cloudy swelling and fatty degeneration. The peritoneal surface was covered by a scanty amount of fresh fibrinous exudate. Infarction of the transverse and descending colon and thrombosis of the superior mesenteric vein were found. The heart was enormously enlarged, weighing 600 Gm., as the result of marked hypertrophy and dilatation of the left ventricle and hypertrophy and moderate dilatation of the right ventricle. The epicardial surfaces were smooth and glistening. The mitral valve was normal. There was no stenosis of the ostium or insufficiency of its leaflets. The aorta and the aortic valves were the seat of a syphilitic aortitis and sclerosis. The syphilitic process in the aorta involved the entire arch but was most marked in the ascending portion and sinuses of Valsalva. A great deal of sclerosis and calcification were also found in this area. The aortic valve cusps were markedly thickened, shortened and retracted. Their edges were rounded, and there was a slight separation of two of the commissures. The posterior cusp was unusually rigid and calcified in the diastolic phase, thus projecting into the aortic lumen. Both of the coronary

orifices were patent. At the level of the aortic ring the vessel measured 9.5 cm. in circumference. The valve was both relatively and absolutely insufficient. The tricuspid and pulmonary valves were grossly normal. The coronary arteries were moderately sclerotic, but there was no evidence of coronary occlusion.

COMMENT

My attention was first drawn to the possibility that an organic lesion might be the mechanism for the production of a Flint murmur while I was working in Vienna under Prof. J. Erdheim. There I had the opportunity to study at autopsy several cases in which the Flint murmur had been heard, and I was impressed by the fact that in these cases, associated with the aortic insufficiency, there occurred as a part of the aortic involvement vegetations of large size on the posterior aortic cusp. The first case described in this report is of such a nature, while in the second the same mechanical effects were produced by another sort of aortic lesion. The common factor and the method by which it produced the Flint murmur would seem to be as follows:

During the systolic contraction of the left ventricle, the aortic cusps with any vegetation that may be superimposed on them are forced up into the aorta. During diastole the valves recede, projecting outward and downward, and attempt to approximate along their ventricular surfaces. Under these conditions a vegetation suspended from the ventricular surface of the posterior aortic cusp will rest on or near the endocardial surface of the ventricle. This vegetation is now occupying the normal diastolic mural position of the anterior leaflet of the mitral valve. Therefore, the vegetation does not permit the anterior mitral leaflet to rest on or near the ventricular wall, but instead holds it up and at the same time produces a bulge with the formation of a culdesac on the auricular surface of the anterior flap of the mitral valve. It is this deformity of an otherwise intact mitral leaflet that produces the eddies and currents which give rise to a Flint murmur (fig. 2).

In case 1 such a mechanism occurred, and it is to be noted that the presystolic murmur was present before signs of aortic regurgitation occurred. This fact strongly suggests that it was the vegetation on the posterior aortic cusp that played the important rôle in the mechanism of the Flint murmur and not the regurgitation which later occurred with the progress of the destructive lesion. The latter is the mechanism suggested by Herrmann,² although he mentioned that bulging of the posterior segment may in some instances encroach on the mitral orifice and at least at times contribute some to the obstruction of the orifice.¹¹

11. In reviewing one of Herrmann's earlier contributions (*Am. Heart J.* 1:485, 1926), one is impressed with the fact that the Flint phenomenon occurred in 20 per cent of the dogs with experimental aortic insufficiency and that spontaneous endocarditis also appeared in 20 per cent of the experiments.

In cases of healed endocarditis or arteriosclerosis of the aortic cusps and occasionally in syphilis of the aorta in which the aortic cusps are secondarily involved as a result of the syphilitic valvulitis, the secondary changes of sclerosis and calcification that have taken place in the valve cusps cause them to project into the lumen of the aorta, since they are calcified in a permanent diastolic phase. The same sort of deformity of an intact mitral leaflet as that described in the first case may therefore be produced, as was observed in the case of the vegetative lesion. Thus in case 2 it was demonstrated at necropsy that when the anterior mitral leaflet was in its diastolic position a bulge and a culdesac were produced on the auricular surface of the anterior mitral leaflet by the calcified projecting posterior aortic cusp.

In considering the description of the Flint murmur as it is given in textbooks and in published reports, one is impressed with the fact

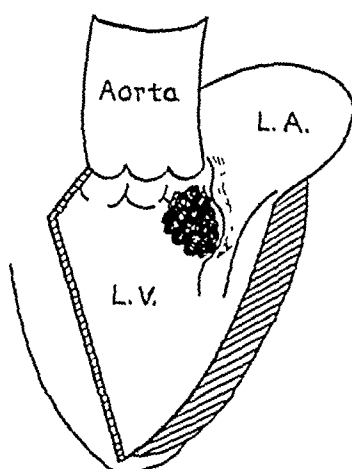


Fig. 2.—Diagrammatic representation of the relation of the vegetative mass on the aortic valves to the intact anterior leaflet of the mitral valve. The culdesac and eddies produced by it account for the Flint murmur.

that the term "blubbery presystolic murmur" has been much overused if not abused and has come to be a rubber-stamp expression that is commonly applied to a large and poorly defined group of audible phenomena. Phear,¹ who studied many cases both clinically and pathologically, mentioned that the murmur may occupy the beginning, middle or end of the diastolic period. Osler¹² spoke of it as extremely variable in intensity, disappearing and reappearing without apparent cause. In this regard it is apparent that by my interpretation of the mechanism of its production differences in the size and position of the vegetation on the aortic valve in its relation to the anterior mitral leaflet would necessarily cause a variation in the size and position of the culdesac on

12. Osler, W.: *Principles and Practice of Medicine*, ed. 3, New York, D. Appleton and Company, 1898, p. 714.

the auricular surface of the mitral leaflet. This variation in size of the vegetation, due to rapid growth in some cases and partial or total loss from embolization or rupture of aortic cusps in others, would explain the extreme variability of the murmur and particularly its disappearance and reappearance.

Although the original and the previously given modified explanations of the mechanism of the Flint phenomenon are possible, they are not based on demonstrable pathologic and anatomic changes, and this fact, associated with the vagueness of the clinical definition of the murmur, greatly weakens the value of this phenomenon for the clinician. If only one type of this murmur, therefore, can be established as caused by variation in anatomic structure, such as is described in my two cases, it would seem that it can be definitely removed from the group of poorly understood functional murmurs and included in that of the important organic murmurs of morphologic significance.

CONCLUSIONS

One cause of the Flint murmur is a mechanical deformity or distortion of an otherwise essentially normal anterior flap of the mitral valve.

The deformity consists of a bulging of the anterior mitral leaflet with the formation of a culdesac on the auricular surface. This may be produced by a vegetation on the posterior aortic cusp or by a calcified posterior cusp stiffened and fixed in its diastolic phase.

Various aortic diseases may produce this deformity, such as bacterial infection, active or healed, arteriosclerosis and occasionally syphilis of the aorta, if it is complicated by secondary involvement and sclerosis of the aortic cusps.

Laboratory Methods and Technical Notes

A NEW NEGATIVE MASS FOR MAKING ACCURATE PLASTIC REPRODUCTIONS

PAUL GROSS, M.D., CLEVELAND

The method of Poller¹ enables an amateur with only a moderate amount of skill to make presentable plastic reproductions of any part of the body and of inanimate objects with a surprising degree of accuracy and minuteness of detail. The method has the following advantages over other methods: It is simple and easy to execute. Irregularities and undercutting in the contours of the object to be reproduced, even though of high degree, do not hamper the worker. Indeed, often it is possible to make a one-piece mold. It does not require any preparation of the skin and will not tear out hair. It is possible to reproduce the face of a living person with the eyes open. The preparation is sterile and is applied at body temperature. The method can therefore be used to reproduce open lesions. It has, however, been commercialized; the formulas have been kept secret and the materials made expensive.

It is the purpose of this paper to present a different and new negative mass which is cheap and easily prepared and which yields satisfactory results.

PREPARATION OF THE NEGATIVE MASS

The negative mass consists of agar, magnesium soaps, absorbent cellulose wadding and water in the following proportions:

Material	Parts by Weight
Agar	100
Oil soap	100
Magnesium sulphate	40
Absorbent cellulose wadding*.....	12
Water	700-800

(this is variable: see text)

* The cellulose wadding from the so-called sanitary napkins or pads was used.

The agar is heated in about 2,000 cc. of water until it is completely dissolved. The cellulose wadding is macerated in hot water until the fibers have separated. It is then thoroughly stirred into the hot agar. The oil soap is next added, and when it is completely dissolved and incorporated into the agar mass, a concentrated solution of the magnesium sulphate is slowly poured into it. At the same time, the mass is vigorously stirred. This precipitates the insoluble magnesium soaps. The

From the Laboratory of Charity Hospital and the Institute of Pathology, Western Reserve University.

1. Poller, A.: *Das Pollersche Verfahren zum Abformen*, Berlin, Urban & Schwarzenberg, 1931; *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **13**:391, 1929. Iglauer, S.: *Laryngoscope* **42**:774, 1932. Kaempfer, L. J.: *Hygeia* **10**:636, 1932.

mass solidifies at about body temperature. The solid material is chopped fine or, preferably, ground in a food grinder. Since this mass contains from two and one-half to three times too much water, it is spread out thinly on paper and allowed to dry at room temperature to a state in which the crumbs are distinctly moist but no water can be expressed. The material is then ready for use.



Fig. 1.—Death mask cast in plaster of paris out of a one-piece mold. This illustrates the minuteness of detail obtainable.

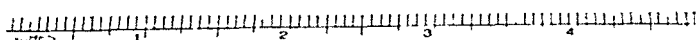


Fig. 2.—Skull of an anencephalic fetus cast in plaster of paris out of a three-piece mold. The skull to the left is the original. The plaster of paris copy is to the right. This illustrates the use of a relatively simple mold to reproduce a very complicated rigid structure.

PREPARATION OF THE MOLD OR NEGATIVE

The ground material is heated in an enameled pan or dish under constant stirring to avoid burning. The consistence is adjusted by adding water or by evapora-

tion to that of a moderately thin paste which will allow itself to be applied with a brush without lumpiness and yet be viscous enough not to flow off dependent surfaces. The first layer of the material is applied thinly with a heat-resistant brush² at a temperature which produces no discomfort when applied to the cheek. Weak, fragile surfaces such as the hairy scalp are best first brushed delicately with a thinner, more fluid mass to stiffen the surface which will support the subsequent thicker negative mass. After the surface has been well covered with the agar mass by means of the brush, the proper thickness of the mold (from 2 to 4 cm.) is obtained more expeditiously by applying the material with a spatula. Depending on the size of the mold and the thickness of its wall, it may be necessary to reenforce it in order to avoid distortion. A sufficiently thick coat (from 5 to 10 mm.) of plaster of paris has been found satisfactory. No attempt should be made to remove the mold until the agar mass has completely hardened. The removal should be done with care and the vacuum broken gradually. Since the agar mass tends to lose water to the air, distortion is likely to result unless the positive is made within a reasonable time or unless the mold is kept properly moist.

Absorbent surfaces must be made nonabsorbent by painting with paraffin-benzene solution or other means to prevent the negative material from adhering. Similarly, if formaldehydized material is to be modeled, the specimens must first be washed free from formaldehyde. Then the surface is coated with glycerin or linseed oil in order to facilitate separation of the mold from the specimen. When a complete hand is to be modeled, the mold can be slipped off like a glove, since the agar mass is resilient. It is advisable to make cuts into the medial and lateral borders of the mold at the wrist previous to an attempt to remove the mold from the hand. Adult feet, entire heads, arthritic hands and other complicated structures are best made by splitting the mold into component parts, removing these components separately and reassembling them. The manner of splitting a mold must be left to the discretion of the worker. It is suggested that this be done by placing strong threads in appropriate positions before the agar mass is applied, and cutting the solidified agar mass by means of these. It occasionally occurs that in removing the mold from the original, pieces of the mold crack off. These pieces are replaced and fastened by means of long, slender pins, such as those used for mounting insects.

PREPARATION OF THE POSITIVE OR CAST

Plaster of paris has been used more than any other material for the positive, largely because of its cheapness. It has its disadvantages, but on the whole this material has proved satisfactory. When working with plaster of paris, it is necessary to adjust the fluidity so that it can be poured into and out of the mold several times and yet is not so thin as to entrap tiny air bubbles in doing so. Enough time must be given for the plaster to set, since the plaster in contact with the agar mass sets slowly, and premature removal of the mold may destroy the finer details. Red sealing wax has also been used successfully. It is rendered more fluid by the addition of a small amount of turpentine, which also lowers the melting point of the substance. The addition of an excessive amount of solvent renders the sealing wax soft and sticky. It seems likely that white sealing wax, though more expensive, would be more satisfactory, since it can be tinted by the addition of pigments and is more easily painted. The sealing wax is painted on the impression surface with a heat-resistant brush at a temperature which is no higher than is necessary to

2. A brush the bristles of which will not fall out and will remain moderately stiff in hot water.

keep the sealing wax at the proper fluidity. Paraffin has also been used. The agar mass separates easily from the positive. If the cast possesses markedly undercut surfaces, the mold is usually broken in removing the cast, and it becomes difficult to make a second cast from the same mold.

After use, the agar mass is ground up and stored in moisture-retaining containers until it is to be used again. The limit to the number of times that the agar mass can be reused has not been found.

COMMENT

The salient features of the method lie in the resiliency and other properties of the agar negative mass. Agar alone is too fluid to remain on dependent surfaces and tends to fracture too easily. To remedy the tendency to fracture, the absorbent cellulose wadding is introduced. Examination of a fractured surface of the negative mass discloses innumerable fine fibers of cellulose protruding, which act as a binding agent. This material also diminishes the tendency of the agar to flow. In preliminary experiments, a coarse material, such as chalk, was used to give the mass more body. However, chalk impaired the resiliency of the mass and made it more friable. Magnesium soaps were found satisfactory. At room temperature, the magnesium soaps are sticky solids which, when precipitated about cellulose fibers, will closely bind these together. At high temperatures, the soaps become fluid. It appears that the magnesium soaps not only give body to the mass, but also add to its strength.

SUMMARY

A method for making accurate plastic reproductions is described in which the negative material is cheap and easily prepared. The negative material consists of an agar-gel-soap-cellulose wadding mixture. The advantages of this method are enumerated. The positive can be cast in plaster of paris or paraffin, or made of resinous compounds such as sealing wax. The negative material can be used repeatedly.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—J. P. Simonds, professor of pathology in Northwestern University, has accepted the appointment as state chairman for Illinois of the American Society for the Control of Cancer.

Robert Rössle, professor of pathology in the University of Berlin, is now the editor of *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*.

Lee Foshay has been made associate professor of research bacteriology in the college of medicine of the University of Cincinnati.

Nathan Chandler Foote, formerly professor of pathology in the University of Cincinnati, is now professor of surgical pathology in Cornell University Medical College, New York, and surgical pathologist to the New York Hospital.

Amos C. Michael has been appointed instructor in pathology in the medical school of the University of Indiana at Indianapolis.

Louis H. Braafladt, formerly professor of pathology in Shantung Christian University, Tsinanfu, China, and recently hospital pathologist in Minot, N. D., died in North Sacramento, Calif., on Nov. 10, 1933, of staphylococcic septicemia, at the age of 48.

Emile Roux, the last to survive of Pasteur's collaborators, and the most intimate, died on Nov. 3, 1933, at 80 years of age. He was Pasteur's preparator from 1878 to 1883. In 1904 he followed Duclaux as director of the Pasteur Institute in Paris. With Yersin he discovered diphtheria toxin in 1888 and thus made possible the discovery of diphtheria antitoxin by Behring. Of extreme simplicity, he devoted himself unreservedly to carrying forward microbiologic investigation in Pasteur's spirit.

Pathologic Institutes Opened.—The Mallory Institute of Pathology of the Boston City Hospital was opened formally on Dec. 13, 1933. In the evening a dinner took place in honor of Frank B. Mallory.

The Algernon Firth Pathological Institute of the University of Leeds has been opened. The institute includes departments of pathology, bacteriology and cancer research. It is hoped that a pathologic museum may be added later.

Award for Essay on Goiter.—The American Association for the Study of Goiter offers \$300 for the best essay based on original research on any phase of goiter, presented at the annual meeting in Cleveland, June 7, 8 and 9, 1934. Manuscripts, in English, must be submitted to the corresponding secretary, J. R. Young, M.D., 670 Cherry Street, Terre Haute, Ind., not later than April 1, 1934.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE THYROID GLAND OF THE WHITE RAT EXPOSED TO COLD. A. T. KENYON, *Am. J. Path.* **9**:347, 1933.

Exclusion of light for periods of from ten to twenty-five days did not produce striking changes in the thyroid gland of the rat. In confirmation of the work of Cramer, Ludford and Mills, exposure of rats to cold for from ten to twenty-five days produced hypertrophy, hyperplasia, loss of colloid and increased vascularity in the thyroid gland. Iodine in doses of 10 γ (gamma 0.001 mg.) daily diminished or prevented the change. Hypertrophy and loss of colloid in general mean preponderant excretion of the hormone from the thyroid gland, arising either from impaired formation or from excessive excretion of the hormone. The actual amount excreted must be determined on physiologic grounds. There are no good reasons for supposing that impaired formation of the hormone occurred in these experiments. It is likely that the hypertrophy and loss of colloid herein described signify that the thyroid gland was excreting more of its hormone, but the essential demonstration by the tissues of increased need for thyroxine is as yet lacking.

AUTHOR'S SUMMARY.

INFLUENCE OF VARIATIONS IN FLUID INTAKE ON INTRACRANIAL PRESSURE IN "EPILEPTICS." FRANK FREMONT-SMITH and H. HOUSTON MERRITT, *Arch. Neurol. & Psychiat.* **29**:454, 1933.

Fremont-Smith and Merritt studied the effect of rapid drinking of large quantities of water on the intracranial pressure when diuresis is normal or inhibited. They also studied the effect of excessive and limited amounts of drinking fluids on the intracranial pressure in patients suffering from repeated generalized convulsions. They concluded that the cerebrospinal fluid pressure was not appreciably influenced by rapid drinking of large amounts of water when diuresis was normal, but when the excretion of urine was prevented by pitressin, a definite rise in the intracranial pressure was obtained. In prolonged periods of liquid intake, no rise of spinal fluid pressure was obtained from ingestion of large quantities of water, for the kidneys regulate the large or small intakes. No decrease in pressure was caused by restriction of fluid intake. Restriction of fluids may cause diminution of the number of epileptic attacks, though the authors believe that this diminution is brought on by the variations in the cerebrospinal fluid pressure.

G. B. HASSIN.

DEVELOPMENT OF THE MENINGES. SAMUEL C. HARVEY, HAROLD S. BURR and ERNEST VAN CAMPENHOUT, *Arch. Neurol. & Psychiat.* **29**:683, 1933.

By implantation of the prosencephalons of chicks on the allantois of a one hundred and ninety-two hour host without and with neural crest cells, selective staining of the neural crest with Nile blue sulphate and heteroplastic transplantations of the neural crest of the frog, the authors tried to add new proofs that the pia is an ectodermal structure derived from the neural crest, and that the pachymeninx is a mesodermal formation derived from the mesenchyme.

G. B. HASSIN.

THE SUBDURAL SPACE AND ITS LININGS. TIMOTHY LEARY and EDWARD A. EDWARDS, *Arch. Neurol. & Psychiat.* **29**:691, 1933.

Comparative studies of the scraped linings of the pericardium, pleura and subdural cavity convinced Leary and Edwards that the structures of the fore-

going cavities are not alike, that the dura is lined by fibroblasts and not mesothelial cells and that the arachnoid portion of the subdural space is covered by ectodermal cells.

G. B. HASSIN.

RECOVERY OF SENSATION IN DENERVATED PEDICLE AND FREE SKIN GRAFTS.

F. E. KREDEL and J. P. EVANS, *Arch. Neurol. & Psychiat.* **29**:1203, 1933.

Kredel and Evans utilized skin grafts in their transplantations for the study of regeneration of nerves. The question as to whether a divided nerve regenerates from the central or peripheral stump has been extensively studied histologically, mainly in animals. The studies of Kredel and Evans are practically the only careful observations along these lines in human beings, and they furnish an indirect proof of the correctness of the central theory of regeneration of nerves. The free as well as the pedicle skin grafts (on the lips and the extremities) showed in seventeen of eighteen cases studied a return of the various sensations—pain, temperature and touch—regardless of the types of grafts used. Sensation reappeared as early as three weeks and as late as eleven years after transplantation, and the areas which showed recovery of sensation were about the periphery of the flap at the border of the proximal (central) nerve supply; that is, the recovery of sensation progressed, in the cases studied, from the center to the periphery. The sensation of pain returned first, that of touch next, and the discrimination of temperature last. The authors emphasize the important fact that a regenerating nerve does not follow the Schwann cells of the peripheral nerve, as its fibers in their cases were not parallel to those of the nerves of the transplant.

G. B. HASSIN.

REACTION OF CEREBRAL TISSUE TO DIRECT INJECTION OF OIL. C. R. TUTHILL, and G. M. BECK, *Arch. Neurol. & Psychiat.* **29**:1263, 1933.

Neuroglial and microglial reactions of the brain have been studied by Tuthill and Beck after the direct introduction of rabbit fat and mineral oil or olive oil into the brains of rabbits. Eleven rabbits were killed at intervals of from twenty-four hours to fifty-one days after the injections of sterile oil into the brain substance. A remarkable phenomenon occurred after the skulls were opened; oil flowed freely from the cerebral surfaces, along the cranial nerves and, on section, from the ventricles. In the meninges macrophages were scarce and, before ten days, very rare; the oligodendroglia were swollen (after twenty-four hours) but did not produce fat granule cells. Astrocytes also exhibited an early reaction—a partial loss of processes near the margin of the wound, where on succeeding days they became hypertrophied, especially in the surrounding nerve tissue. After fifty-one days the injured area was closed by a straight line of hypertrophic astrocytes, while connective tissue fibers in that area were few. Newly formed capillaries were present early—in old wounds from three to five days. Microglia cells were increased, and the capillaries nearest the wound were stripped of microglia twenty-four hours after the injection of oil. The authors emphasize the relation of the microglia to the blood vessels and believe that they have demonstrated transformation of adventitial wall cells into microglia.

G. B. HASSIN.

EFFECTS OF BLOOD LOSS ON ERYTHROID CELLS IN THE RABBIT MARROW. B. F. STEELE, *J. Exper. Med.* **57**:881, 1933.

The relative proportion of the various sorts of erythroid cells of the bone marrow has been determined after acute and chronic hemorrhage and after damage to the marrow with acetyl-phenylhydrazine. The normal erythroid pattern shows megaloblasts and erythroblasts in the lowest percentage, then normoblasts, reticulocytes and mature erythrocytes, respectively, in increasing proportions. All three states studied show an increasing shift to the left to a condition after

damage by acetyl-phenylhydrazine, in which the erythroblasts and megaloblasts exceed the mature erythrocytes. The marrow pattern finds direct expression in terms of the cells of the blood.

AUTHOR'S SUMMARY.

INCREASE IN GONADOTROPIC EFFECTS OF HYPOPHYSEAL EXTRACTS. H. M. EVANS, M. E. SIMPSON and P. R. AUSTIN, *J. Exper. Med.* **57**:897, 1933.

The increased gonadotropic effect obtained by combining the follicle-ripening hormone of the anterior pituitary body with hypophyseal extracts can be secured equally well by the use of preparations which contain high amounts of the growth-stimulating or of the gonad-stimulating hormone. In hypophyseal extracts containing the growth hormone, the synergistic effects do not parallel the content of growth-promoting substance. Similarly, in hypophyseal extracts containing the gonad-stimulating hormone, the synergistic effects do not parallel the content in the gonadotropic factor. The hypophyseal substance involved has been prepared sufficiently free of the growth and gonad-stimulating hormones to make it inadmissible to consider either of these substances as responsible for the reaction.

AUTHORS' SUMMARY.

EXPERIMENTAL GRANULOPENIA. E. W. DENNIS, *J. Exper. Med.* **57**:993, 1933.

Pyogenic organisms, under conditions simulating a focal infection, are capable of producing in rabbits a granulopenia which may cause generalized infection and death. It is suggested that agranulocytosis in man is due to the action of leukocidin, rather than to a specific micro-organism.

AUTHOR'S SUMMARY.

THE SUPRARENAL CORTEX IN SUPRARENAL INSUFFICIENCY IN THE DOG. G. A. HARROP ET AL., *J. Exper. Med.* **58**:1 and 17, 1933.

The basal oxygen consumption, respiratory quotient, blood flow, blood pressure and the changes in the concentration of the arterial blood were determined in suprarenalectomized dogs (*a*) when they were receiving injections of cortical extract (Swingle-Pfiffner), (*b*) during suprarenal insufficiency induced by withdrawal of the injections and (*c*) during the period of recovery brought about by resumption of the injections of extract. Reasons are advanced for the view that the hemoconcentration which occurs is probably due to loss of fluid through the kidneys, rather than by increased capillary permeability and loss into the tissues, or by loss through the gastro-intestinal tract. The loss of fluid from the plasma and tissues will explain the symptoms which follow withdrawal of injections of the hormone, as well as the fatal outcome. The assumption that the suprarenal cortex or its hormone has a detoxifying action on some product of metabolism is thus rendered unnecessary.

A characteristic alteration in the electrolyte structure of the blood plasma of the suprarenalectomized dog occurs when injections of cortical extract are stopped. This alteration progresses during the course of the suprarenal insufficiency, parallel with the hemoconcentration and the loss in weight. When injections of cortical extract are resumed, the electrolyte structure returns to its original form, the alterations paralleling the dilution of the blood and the return of the body weight to its original level. The hemoconcentration, with the resulting physiologic changes which take place in the suprarenalectomized dog after the cessation of injections of cortical extract, is associated with a loss of sodium and chloride, accompanied by their proper complement of body water, by way of the kidney. Since this effect is produced in the suprarenalectomized animal that is well nourished and in excellent condition solely by the cessation of the injections of the cortical hormone and since the reverse process of repair of the losses of electrolytes and water can be affected solely by resumption of the injection of extract, it follows that all of the observed phenomena are due to this cause, and to this alone. It can be concluded that one function of the cortical extract in the suprarenalectomized dog is that of participa-

tion in the regulation of the sodium and chloride metabolism and, consequently, of the balance and distribution of water. The loss of water, in the absence of the cortical hormone, is sustained partly by the blood plasma, but to a far greater extent by the interstitial body fluid. The available evidence points to the kidney as the locus of this regulatory function of the cortical hormone.

AUTHORS' SUMMARIES.

Pathologic Anatomy

THE PATHOLOGY OF PSITTACOSIS IN MAN. R. D. LILLIE, Nat. Inst. Health, Bull. 161, 1933.

Psittacosis in man is characterized anatomically by a pulmonary inflammatory process which usually goes on to consolidation. Consolidation is primarily focal or lobular, and not especially related to the bronchioles. It often becomes confluent, but even when grossly lobar it shows histologic evidence of its primarily lobular nature. An apparent sequence of congestion and edema, red hepatization, or, better, splenization, and gray hepatization may be observed, but all stages are commonly seen in one case. Histologically, fibrin, red cells, polymorphonuclear leukocytes and epithelial cells appear early in the exudate; fibrin disappears, red corpuscles decrease in number, and leukocytes are replaced by large mononuclear phagocytes and epithelial cells. The alveolar epithelial cells undergo swelling, fatty degeneration and desquamation, with an apparent increase in their numbers, and may be invaded by rickettsiae. In the earliest stages interstitial infiltration is lacking, but a serous exudate soon appears and is later replaced by lymphocytes, large mononuclear cells and occasional tissue mast cells. Necrosis of the septums is sometimes seen. The bronchioles may remain clear, or may contain a serocellular exudate similar to that in the adjacent alveoli. Pleural reaction is relatively infrequent and usually of minor grade. The lymph glands show swelling, vacuolation and phagocytic activity of the sinus endothelium, followed by desquamation and then necrosis of macrophages. The spleen is ordinarily moderately enlarged, soft and congested, and tends to be smaller when gray hepatization of the lung predominates. Histologically, the prominent findings are congestion, infiltration of the pulp by lymphoid cells and an increase in fixed and free phagocytes, sometimes with erythrophagia. In the liver, swelling, vacuolation and phagocytic activity of the Kupffer cells are often found. Focal coagulation necroses of the parenchyma have been found in about a third of the cases, and granulomas, such as have been observed in parrots, were seen in one case. This last case also showed a focal necrosis of the suprarenal cortex. The changes in the heart muscle and kidney are assignable to parenchymatous degeneration, which is usually of moderate grade only. Similarly, Zenker's degeneration and hemorrhages in the body musculature have been reported in a number of cases. Punctate hemorrhages have been seen in the brain substance, in the serous membranes, in the mucosa of the renal pelvis and, rarely, in the subcutaneous tissues. Venous thrombosis has been an occasional complication. This report is based on the published records of autopsies in psittacosis and on nine cases studied histologically by the author, covering a total of fifty-two cases.

AUTHOR'S SUMMARY.

PERFORATION OF THE GASTRO-INTESTINAL TRACT BY BARIUM SULPHATE MEALS. W. HIMMELMANN, München. med. Wchnschr. 79:1567, 1932.

Thirty-nine cases in which a barium sulphate meal perforated the gastrointestinal tract have been recorded, and the author adds to these one of carcinoma of the stomach, one of chronic peptic ulcer, two of ulcer of the duodenum and one of a strangulated loop of the ileum, in which this accident occurred.

EDWIN F. HIRSCH.

A CASE OF PARIETOFRONTAL CRANIOPAGUS. C. BLUMENSAAT, *Virchows Arch. f. path. Anat.* **285**:140, 1932.

This unusual example of symmetrical double monstrosity, in which the twins were broadly united by their corresponding parietofrontal regions, is of interest because the children lived from February 2 to April 8. During life they exhibited distinct individualities. One had pneumonia and died eight hours before the other. Separation was considered, but roentgen examination revealed that the subdural spaces communicated widely with each other. The two brains were in close apposition, being separated only by pia, the two layers of which were united in places. The brain of the twin who died first revealed histologic evidence of postmortem change.

O. T. SCHULTZ.

REACTIONS OF LYMPH NODE GROUPS IN DYSCRASIAS OF THE BLOOD. M. NORDMANN, *Virchows Arch. f. path. Anat.* **285**:201, 1932.

In previous studies Nordmann has propounded the thesis that, according to the degree of their normal resorptive functional activity, the lymph node groups may be divided into peripheral (axillary and inguinal), central (celiac and periaortic) and intermediate (cervical and mediastinal). In this paper of seventy-nine pages he seeks to establish his view more thoroughly by presenting a study of the reactions of the various groups of nodes in a variety of dyscrasias of the blood. The material for the study, with the number of cases, was: transfusion, 29 (single, 9; multiple, 8, and experimental in the guinea-pig, 12); agranulocytosis, 6; secondary anemia, 13; pernicious anemia, 3; hemolytic icterus and congenital anasarca of the new-born, 1 each; leukemia, 10 (congenital myeloid, 2; adult myelocytic, 4; adult myeloblastic, 2, and lymphatic, 2). The study consisted in a comparison of similar lymph node groups in the different conditions and study of different groups in each case. In the resorption of blood, especially after transfusion, the lymph nodes act as secondary blood filters, and according to their activity in this respect they may be graded from most active to least active into the following series: celiac, periaortic, mediastinal, cervical, mesenteric, axillary and inguinal. In the various conditions selected for study, the degree of reaction in the various groups in general follows the same sequence. In agranulocytosis, Nordmann recognizes two types of lymphoid reaction, an aplastic and a hyperplastic, depending in part on the age of the subject and in part on the duration of the disease. In this connection it is to be noted that the clinical duration of the final attack of agranulocytosis in the six cases studied varied from six to thirty-two weeks, which is considerably longer than that of the usual case of agranulocytosis. In secondary anemia the lymph nodes are the seat of simple reticular induration or simple lymphoid hyperplasia. Cellular or fibrous sinus catarrh, depending on the duration of the disease, characterizes the nodes of pernicious anemia. Sinus catarrh is defined as a filling of the sinuses by proliferated endothelium and reticulum cells, the proliferative stage being followed by fibrosis. Pernicious anemia is also characterized by moderate myeloid transformation, the degree of which in the various groups follows the usual serial order. The histologic evidence indicates that the myeloid transformation occurs in the sinuses. In the case of hemolytic icterus the nodes revealed both myeloid and erythropoietic transformation, varying in the usual serial sequence in the various groups. The lymphoid tissue was undeveloped in the case of congenital anasarca, and myeloid transformation was not observed. In congenital myeloid leukemia the nodes revealed marked myeloid transformation, which followed the usual sequence in the various groups. The same is true of adult myelocytic leukemia, except that the rule of sequence may be broken and local groups of nodes that are subjected to greater resorptive functioning may present the more extreme grades of myelopoiesis. Myeloblastic leukemia may present a histologic picture like that of lymphatic leukemia. In intermediate forms of myeloid leukemia, the degree of differentiation of the myeloid cells in the various groups follows the usual serial order. O. T. SCHULTZ.

SENILE CHANGES IN THE INFERIOR VENA CAVA OF BOVINES. C. KRAUSE and X. IWANOFF, *Virchows Arch. f. path. Anat.* **285**:343, 1932.

In a second study of the vascular lesions of domestic animals the authors examined the inferior vena cava of 300 cattle and 200 domestic buffaloes of different ages. The normal histologic structure of the thoracic portion of the vessel differs from that of the abdominal portion. No changes were noted in the first named portion, but the abdominal portion was uniformly the seat of a senile sclerotic process in animals more than 10 or 12 years old. The process was characterized by fibrosis of the inner portion of the wall with replacement of muscle in this part of the wall by connective tissue. The collagenous tissue of the adventitia was increased, and the adjacent muscle was hypertrophied. Fatty change, necrosis and calcification were not seen except at the mouths of the renal and suprarenal veins, where there occurred changes similar to those caused by the repeated intravenous injection of epinephrine.

O. T. SCHULTZ.

UNUSUAL AORTIC LESION IN A NURSING. K. WOLFF, *Virchows Arch. f. path. Anat.* **285**:369, 1932.

An infant who died on the twelfth day after birth presented during life the following syndrome: malformation of the right ear, cloudiness of the cornea, cyanosis and a greatly enlarged heart. The antemortem diagnosis was congenital malformation of the heart. The Wassermann reaction of the infant and that of the mother were negative, and gross and histologic examination revealed no evidence of syphilis. At necropsy the heart was found to be enlarged but devoid of developmental errors. In the ascending, transverse and descending portions of the aorta were seen narrow, cleftlike areas that had the appearance of tears. The lesions ceased abruptly just below the diaphragm. Microscopic examination revealed as the earliest lesions poorly defined, irregular areas in the media, in which the elastic fibrils had disappeared. The collagen fibers were swollen and had also in part lost their identity. Muscle tissue was apparently the last element to be altered; the areas contained muscle nuclei in various stages of degeneration. The ground substance had the staining reaction of mucoid degeneration. The surface of the intima was intact over the lesions. Most striking was the absence of any reparative or cellular infiltrative reaction of the tissues in or about the lesions. In the macroscopic tearlike lesions also, reactive phenomena were entirely wanting. The material resulting from the degeneration of the elastic and other tissues of the media had apparently been absorbed, and the intact intima had been folded into the defect thus produced. The small vessels were normal. The lesion described is most like that which Erdheim has described in the aorta of elderly persons as the cause of spontaneous rupture of the aorta, but which has not hitherto been seen in the earlier periods of life. In the case described no cause for the lesion could be found.

O. T. SCHULTZ.

PATHOLOGIC HISTOLOGY OF ACUTE ORCHITIS IN MUMPS. C. MANCA, *Virchows Arch. f. path. Anat.* **285**:426, 1932.

Although the literature includes a few reports of the late stages of orchitis in mumps, it contains, according to the author, no description of the acute stage of this complication. A 21 year old soldier became severely ill with bilateral mumps. On the fourth or fifth day after the onset the left testis became swollen and painful, and a few days later the right testis was involved. Fourteen days after the onset he died of the mumps, necropsy revealing no complicating disease. The earliest stages of the testicular lesion consisted of localized areas of serofibrinous exudation into the intertubular tissue and of leukocytic emigration into the tubules in these areas. Later the areas became confluent, the interstitial tissue became infiltrated by leukocytes, and the walls of the tubules were destroyed. Spermatogenesis had ceased, even where there was no tubular or intertubular inflammatory reaction. The epididymis and vas were free from change. The histologic differ-

ences in the various forms of acute orchitis are discussed. The author believes that the orchitis of mumps can be distinguished histologically from the other forms.

O. T. SCHULTZ.

AN UNUSUAL CASE OF CORPORA AMYLACEA OF THE LUNG. O. SCHILDKNECHT, *Virchows Arch. f. path. Anat.* **285**:466, 1932.

The case reported differs from previous ones in the large number of bodies present in the lung, in their calcification and in their failure to give any of the reactions for amyloid. The patient was a woman who died at the age of 45 of dementia paralytica. The lungs at necropsy were emphysematous and passively congested. Approximately one fourth of the alveoli contained laminated bodies with the morphology of corpora amylacea. A few of these bodies were present in the interstitial tissue. Many were calcified; this had led to a roentgen diagnosis of miliary tuberculosis during life. The bodies gave the microchemical reaction for iron, but none of the amyloid reactions. The author believes that chronic bronchitis and emphysema had led to the collection of a liquid transudate in the alveoli, desquamated cells being admixed with the fluid. This was followed by transformation of the material into a gel and its precipitation about a central nucleus. The author is unable to give an explanation of the calcification and iron incrustation of the bodies.

O. T. SCHULTZ.

CALCIFICATION AND OSSIFICATION OF THE VERMIFORM APPENDIX. A. KRISPER, *Virchows Arch. f. path. Anat.* **285**:481, 1932.

The author could find in the literature only two previously reported cases of calcification and ossification of the appendix. He adds four. In three the appendix had been removed surgically and in one the condition was found by chance at autopsy. In one, calcification and ossification were associated with mucocele owing to occlusion of the lumen by a partly necrotic fibrous polyp. In two, histologic examination revealed that tuberculosis was the cause of the calcification; in one of these bone had been formed. The fourth appendix was completely degenerated and calcified, probably as the result of a previous purulent appendicitis.

O. T. SCHULTZ.

THE CAPSULE OF CYSTICERCUS OF THE BRAIN. A. ANTONOW, *Virchows Arch. f. path. Anat.* **285**:485, 1932.

The structure of the capsule of cysticercus of the brain is dependent on the duration of the infestation. If the duration has been short and the parasite is still alive, the capsule consists of two layers, an inner hyaline membrane and an outer layer of granulation tissue that contains giant cells. After a longer duration and death of the parasite, a third layer of loose connective tissue is laid down internal to the hyaline layer; this layer may contain giant cells. When the dead parasite has been completely broken down, the capsule consists of a single thick layer of dense connective tissue that contains no giant cells.

O. T. SCHULTZ.

REACTIONS OF MESOGLIA IN ACUTE NONPURULENT INFECTIONS OF THE CENTRAL NERVOUS SYSTEM. W. K. BELEZKY, *Virchows Arch. f. path. Anat.* **285**:494, 1932.

In a previous article (*Virchows Arch. f. path. Anat.* **284**:295, 1932) the author presented the evidence that led him to conclude that the mesoglia, consisting of dendritic Hortega cells, oligodendroglia and drainage cells, is of mesodermal origin and corresponds in origin and function to the reticulo-endothelial system of other organs. In acute nonpurulent infections of the central nervous system, such as poliomyelitis, secondary syphilis, spirochetosis and experimental virus diseases, the mesoglia reacts in the same manner as does the reticulo-endothelium of other tissues in these and other nonpurulent infections. The earliest change is swelling

of the oligodendroglia and of the Hortega and drainage cells. Later some of these cells may degenerate and others may proliferate. Proliferation may lead to the formation of focal areas about or near blood vessels, in which cells without processes are transformed into cells with processes; cells of the latter type are derived also from the histiocytes about the blood vessels. Later such areas are transformed into fibrillated glia. The mesoglia reactions are most marked where the action of the infecting agent is most intense, but they tend to be more diffuse than those of the purulent infections of the brain. The reactions are the expression of the protective mechanisms characteristic of reticulo-endothelium wherever it is situated.

O. T. SCHULTZ.

THE SUPRARENAL GLANDS IN TUBERCULOSIS. E. HAUSMANN, *Virchows Arch. f. path. Anat.* **285**:550, 1932.

Both suprarenals were weighed and examined microscopically in sixty-one cases of tuberculosis. The age of the patients varied from 18 to 52 years. There were no characteristic changes in weight or histologic structure, except the presence of tubercles in three cases and of amyloid in eight; in seven of the latter the amyloid infiltration of the suprarenals was part of general amyloidosis.

O. T. SCHULTZ.

TRANSVERSE RIDGES OF THE INNER SURFACE OF THE BRACHIAL ARTERY. J. LEWIN, *Virchows Arch. f. path. Anat.* **285**:704, 1932.

Fine transverse ridges on the inner surface of the brachial artery, which is a muscular artery, have been noted by several observers. In elderly persons the ridge may be replaced by a narrow, shallow depression. To determine the incidence and character of the ridges, a systematic study was made of the brachial artery in 141 necropsies. The ages of the subjects varied from 2 months to over 60 years. The ridges were found to be present even at as early an age as 2 years. They increased in number and frequency with increasing age. Microscopic examination showed that they were due to minute transverse tears of the internal elastic lamella, which were healed by connective tissue. Shrinkage of the scar in the later years of life transformed the ridges into depressions. No changes could be detected in the media or intima that would account for the lesions. They are considered physiologic changes associated with age. Mechanical factors may have a part in their formation.

O. T. SCHULTZ.

LOCALIZED IRON AND CALCIUM INCRUSTATION OF THE SPLEEN. W. BRACKERTZ, *Virchows Arch. f. path. Anat.* **285**:734, 1932.

The spleen that is described by Brackertz was from a woman, aged 23. The clinical diagnosis was cirrhosis of the liver, splenomegaly and possible Banti's disease. The anatomic diagnosis at necropsy was Laënnec's cirrhosis of the liver, chronic splenic tumor and hemochromatosis. In the spleen could be seen a number of small brownish and yellowish nodules. Similar discoloration of the trabecular framework was also noted. Histologically and microchemically these areas had the characteristics of iron and calcium incrustations. The lesions arose in swollen and damaged reticulum fibrils of the pulp and follicles. Such swollen and fragmented fibrils have been described by many authors as mycelia. The calcium deposition is the result of the precipitation of colloidal calcium in a sinus. Fifteen per cent of seventy-six spleens revealed varying degrees of iron and calcium incrustation.

O. T. SCHULTZ.

CHANGES IN PERIPHERAL NERVES AND GANGLIONS IN LARYNGEAL TUBERCULOSIS. A. G. FILATOWA and B. J. LAWREUTJEW, *Virchows Arch. f. path. Anat.* **286**:1, 1932.

In twenty cases of laryngeal tuberculosis, the superior laryngeal nerve, the cervical portion of the vagus and the ganglion nodosum of the vagus were examined

histologically. In eighteen cases the laryngeal involvement was associated with pulmonary tuberculosis; in three cases, portions of the superior laryngeal nerve that had been resected during life were examined. In the nerves and ganglion cells the authors saw changes that they ascribe to long-continued stimulation and irritation of the nerve structures, resulting in growth of axis cylinders and ganglion cell processes. The growth of the axis cylinder leads to a spiral course and to the formation of lateral branches. The newly formed processes of the ganglion cells may have clubbed ends.

O. T. SCHULTZ.

BILATERAL ABSENCE OF VAS DEFERENS WITHOUT RENAL ANOMALY. A. PRIESEL, Virchows Arch. f. path. Anat. 286:24, 1932.

Absence of one vas deferens with anomalous development or absence of the kidney or ureter of the same side is not uncommon. Absence of one vas with contralateral renal defect is less common. Absence of the vas on both sides is extremely rare, the only recorded instance being one reported by the author. In this instance there was dystopia of the right kidney with absence of the left kidney and ureter. Only two cases of unilateral absence of the vas with a normal kidney and ureter on each side have been reported. In the present report the author describes, as the only instance on record, a case of bilateral absence of the vas with a normal urinary system on each side. The man died at the age of 47 of atherosclerosis. The external configuration of the body was of the male type. The testes were large and were in the scrotum. Spermatogenesis was active. The head of the epididymis was present on each side; its tubules were distended by the degenerated products of spermatogenesis. The body and tail of the epididymis, the vas, the seminal vesicle and the ejaculatory duct of each side were absent. The prostate and Cowper's glands were normal.

O. T. SCHULTZ.

A CASE OF PAPILLARY HYPERKERATOSIS OF WALDEYER'S TONSILLAR RING. G. GERSTEL, Virchows Arch. f. path. Anat. 286:116, 1932.

The unusual condition reported was first described in 1873 by B. Fränkel under the name benign lingual and tonsillar mycosis. Death was due to pulmonary tuberculosis in Gerstel's case. On the base of the tongue and in the pharynx, in the region of the lingual, faucial and pharyngeal tonsils that make up Waldeyer's ring, were numerous elevated, rounded and thornlike hyperkeratoses. These arose from the squamous epithelium of the crypts of the lymphoid tissue. The author disagrees with the view of some observers that the condition is a mycosis. No fungi could be seen in the lesions, and the bacteria present were held to be secondary invaders. The process is not inflammatory. It is an epithelial hyperplasia that is sharply limited to the crypts of lymphoid tissue, where multiple localized areas of leukoplakia most often occur.

O. T. SCHULTZ.

MYCOSIS FUNGOIDES WITH INVOLVEMENT OF THE BRAIN AND CRANIAL NERVES. C. MONCORPS and G. BORGER, Virchows Arch. f. path. Anat. 286:157, 1932.

Six and one-half months before his hospitalization lesions of mycosis fungoides appeared on the trunk of a man, aged 35. Five months later the general condition was poor and neurologic symptoms occurred. In the further course of the disease there developed symptoms referable to involvement of practically all of the cranial nerves and others indicative of increased intracranial pressure. Histologic examination at necropsy revealed the presence of infiltrating cellular tissue, similar to that of the cutaneous lesions, in the pia, in the region of the corpora quadrigemina and left caudate nucleus, in both gasserian ganglions and in all the cranial nerves. The degree of involvement of the testis was out of proportion to the clinical and gross anatomic findings.

O. T. SCHULTZ.

CRITICAL SUMMARY OF THE PATHOLOGIC HISTOLOGY OF RHEUMATIC INFECTION.

F. KLINGE, *Virchows Arch. f. path. Anat.* **286**:344, 1932.

In this paper, the twelfth of a series of contributions by Klinge and his associates, Klinge presents a critical summary of the pathologic histology of rheumatic infection. He first states his concept of the disease. It begins as a primary infection of the upper air passages. If the pharyngeal catarrh does not heal within a few days, rheumatic fever results. This disease, in which multiple lesions occur in the various tissues and organs of the body, may manifest itself clinically as rheumatic polyarthritis, as visceral rheumatism or as peripheral rheumatism. After persisting for a number of weeks, the disease may heal, with a variable amount of permanent damage, or it may become chronic. In the chronic stage, which may be articular, visceral or combined, the lesions of the acute stage become cicatrized and new lesions develop. After a variable period of chronicity the disease may heal, usually with considerable permanent damage, or it may become transformed into chronic sepsis. In his summary of the pathologic histology of the disease, Klinge describes the lesions of the various stages and forms of the disease in the various organs or organ systems under the following headings: heart (valves, myocardium, pericardium); blood vessels; tonsils and organs of the neck; joints (synovial membrane; subsynovial, capsular and periarticular connective tissue); skin (nodose rheumatism, erythema multiforme and nodosum); bursae and tendons; musculature; nerves; lungs; liver; spleen; lymph nodes, and kidneys. In whatever organs the lesions may be situated, they begin as focal areas of edema and fibrinoid swelling and degeneration of the ground substance of collagenous connective tissue; the fibrils are not destroyed in the process. To this degenerative process there are added hypertrophy and proliferation of connective tissue cells and lymphocytic and leukocytic infiltration. When the lesions occur in smooth or striped muscle, necrosis of muscle fibers results. In its essential details the rheumatic lesion does not differ from lesions that may be caused by bacteria that do not incite suppuration. The rheumatic process differs from other infectious inflammatory processes in the multiplicity of its lesions, in their widespread distribution throughout the tissues and organs of the body and in the limitation of the early, focal, fibrinoid degenerative process to the connective tissues. The article of forty-five pages has twenty-five illustrations, some of which are in color.

O. T. SCHULTZ.

ACUTE NEPHRITIS AND CORTICAL NECROSIS FOLLOWING SEPTIC ABORTION.

B. ZU JEDDELOH, *Virchows Arch. f. path. Anat.* **286**:389, 1932.

Criminal abortion during the third and the fourth month of pregnancy in two women aged 38 and 19 respectively was followed by sepsis, with acute general peritonitis in one case. Anuria developed and led to death. In each case the kidneys revealed the presence of an intense acute inflammatory process, involving especially the glomeruli, and widespread necrosis of the cortex. The glomerular vessels and the small arterioles were thrombosed. The condition differed from the cortical renal necrosis that occurs usually in the later months of pregnancy in the greater degree of inflammatory reaction. After a discussion of the relation of cortical necrosis to eclampsia, the author concludes that infection was the chief underlying factor in his cases, but that it acted on kidneys susceptible to or already injured by eclamptic intoxication.

O. T. SCHULTZ.

AMYLOIDOSIS IN A NURSING. I. OBERG, *Virchows Arch. f. path. Anat.* **286**:476, 1932.

Amyloidosis is rare in infancy. With the exception of one doubtful case in a child aged 1½ years, the author could find no reference to the occurrence of the condition in children under 4 years of age. The case reported was that of a child, aged 2½ months, who died of pneumococcal meningitis secondary to bilateral otitis media. The gross appearance of the spleen led to an anatomic diagnosis of amyloid disease. The splenic pulp and the glomeruli of the kidney on

microscopic examination contained protein material with the optical and physical properties and the localization of amyloid. The material did not give the characteristic microchemical reactions of amyloid.

O. T. SCHULTZ.

AMYLOIDOSIS AND RETICULO-ENDOTHELIAL REACTIONS IN HORSES USED FOR PRODUCTION OF SERUM. ERNA DOERKEN, *Virchows Arch. f. path. Anat.* **286**:487, 1932.

The tissues of horses that have been used in the production of antitoxic and antibacterial serums offer a material for the study of reticulo-endothelial reactions in immunity. Amyloidosis is said to be frequent and is considered by veterinarians to be the most common cause of death of the animals. Material from one hundred serum horses formed the basis of the study reported. The animals had been used for the production of serum for from two and one-half to fifty-four months. The horses had been used for the production of a variety of antiserums, but the largest number had been used in the preparation of diphtheria and tetanus antitoxins (forty-four and twenty-six, respectively). Amyloidosis was observed in sixty. The percentages of its incidence distribution in the various organs were as follows: spleen, 100; liver, 44; suprarenals, 34; kidneys, 21, and intestines, 12. In eight animals amyloid infiltration led to rupture of the liver and death. Amyloidosis was relatively more frequent in horses used for scarlet fever antiserum than in those used for other antiserums. Reticulo-endothelial reactions, which were present in every animal, were of three types: diffuse hypertrophy and hyperplasia, small granulomatous foci and true granulomas. It was not possible to determine any relation between these types of reaction and the duration of immunization or the kind of serum prepared. Reticulo-endothelial reactions and amyloid infiltration appeared to have a close relationship. The cellular reaction occurred first and was necessary for the production of amyloidosis.

O. T. SCHULTZ.

Microbiology and Parasitology

CERVICO-VAGINITIS OF GONOCOCCAL ORIGIN IN CHILDREN. W. M. BRUNET, D. M. TOLLE, S. A. SCUDDER and A. R. MECALF, *Hosp. Soc. Ser. Mag.*, supp. 1, 1933.

A series of 322 young children with vaginitis of supposed gonococcal origin were studied, 244 with relative completeness. It was found that cervicovaginitis in children does not differ widely from the similar infection in adults. The difference from the adult picture lies in the rarity of inflammation of the vulvo-vaginal glands, of the urethra, of the fallopian tubes and of the peritoneum. Pelvic involvement occurred in only four cases, and infection of the eye in but two, only one of which was gonorrheal. Rectal involvement was rare, and no case of arthritis was observed. Examination of the cervix showed it to be involved in four fifths of the cases, and there was a strong tendency to persistence. Only three cases of the series showed gram-negative diplococci other than gonococci. A differential stain which incorporates the combined features of the original Gram and Pappenheim methods was found to be reliable for the diagnosis of gonorrheal infection. Cultures constituted the most important method of checking up on cases of cervicovaginitis. Fresh rabbit serum, applied at the site of probable primary infection, acted as a provocative in chronic cases in which cultures had become negative.

LUKE W. HUNT.

KENDALL'S MEDIUM. H. M. CARPENTER and P. H. LONG, *J. Bact.* **25**:241, 1933.

Although Kendall's technic was followed minutely, filtrable forms of *Bacillus typhosus* and beta hemolytic streptococci were not produced. It was not possible to cultivate staphylococci from staphylococcus bacteriophage, nor a filtrable coccus from "cold" virus. Diphtheroids and *B. subtilis* were cultivated occasionally from commercial vaccine virus, but in view of the well known observation that these organisms may be contaminants of vaccine virus, no importance was attached to these results.

AUTHORS' SUMMARY.

PNEUMOCOCCUS VARIANTS INTERMEDIATE BETWEEN THE S AND R FORMS. F. G. BLAKE and J. D. TRASK, *J. Bact.* **25**:289, 1933.

Five intermediate variants between type I-S and type I-R pneumococcus have been detected by growing type I-S pneumococci in homologous immune serum broth. They progressively appear and disappear in serial cultures. Two of these, I-b and I-c, were easily stabilized in pure culture. The intermediates between S and R show a progressive and orderly change in their agglutination reactions in homologous and heterologous immune serums. They also show a progressive loss in virulence for white mice. Only one intermediate, II-c, has been derived from type II-S. It was easily stabilized and is comparable to I-c in its agglutination reactions and virulence. The observations described indicate that the dissociation of S pneumococci by growth in homologous immune serum is not a simple S \rightarrow R change but that a considerable number of intermediate variants with fairly well defined characteristics appear and disappear during the process.

AUTHORS' SUMMARY.

THE HISTOLOGICAL CHANGES AND THE FATE OF TUBERCLE BACILLI IN REINFECTED RABBITS. M. B. LURIE, *J. Exper. Med.* **57**:181, 1933.

Immunity to reinfection is a function of the increased capacity of the mononuclear phagocytes to destroy tubercle bacilli and varies directly with the extent of the primary lesion; however, it is rarely sufficient to annihilate completely the micro-organism. This acquired immunity is superimposed on the natural resistance of a given organ. In the presence of sufficient immunity, such as occurs with the persistence of an extensive primary lesion, small numbers of tubercle bacilli are destroyed by the mononuclear cells in situ without local or general infiltration of the tissues by polymorphonuclear or mononuclear leukocytes. Larger numbers of bacilli are destroyed within twenty-four hours by an accelerated formation of sharply localized nodules of mononuclear phagocytes. These progress no further and are absorbed or result in inconspicuous microscopic collections of epithelioid and giant cells. In the presence of less immunity, such as occurs when the primary lesion has almost completely healed, the immediate inflammatory reaction is more intense and diffuse and persists longer. It results in a less rapid disappearance of the bacilli and in a more extensive formation of tubercles. These appear much earlier than in the normal animal and soon resolve. Tubercle bacilli of reinfection may be destroyed even though the primary lesion in the lung and kidney is progressive. This is due to an unhindered extracellular multiplication of the bacilli in the caseous foci that undergo softening and excavation. Resistance may be overwhelmed by the spread of tremendous numbers of living bacilli from these foci through the bronchi or renal tubules, while the moderate numbers of reinfecting bacilli reaching the organs by way of the blood stream are destroyed.

AUTHOR'S SUMMARY.

SPONTANEOUS CONJUNCTIVAL FOLLICULOSIS OF MONKEYS. P. K. OLITSKY and J. R. TYLER, *J. Exper. Med.* **57**:229, 1933.

Spontaneous folliculosis of *Macacus rhesus* monkeys, a type of follicular conjunctivitis associated with marked, local, inflammatory reactions, is apparently a disease sui generis, due to a specific infectious agent. It can be transmitted from monkey to monkey by means of subconjunctival injection of suspensions, and by conjunctival swabbing of the secretions, of affected tissues, or by contact of normal animals with monkeys with folliculosis. The agent causing folliculosis has failed in our hands to pass through Berkefeld and Seitz filters, even those of an unusual degree of permeability; and the lesions that it causes show no cellular inclusions suggestive of the action of a virus. The condition is due apparently

to an organism of low grade pathogenicity. The essential histopathologic structure corresponds to that of a folliculoma which, while not identical with a granuloma, bears certain resemblances to the latter. The studies here reported concern only one species of monkey, *Macacus rhesus*. Further investigations will be carried out on different species of *Anthropoidea* and other animals.

AUTHORS' SUMMARY.

EXPERIMENTAL AVIAN TUBERCULOSIS PRODUCED BY DISSOCIATED VARIANTS OF TUBERCLE BACILLI. W. A. WINN and S. A. PETROFF, *J. Exper. Med.* **57**:239, 1933.

Four variants, S, F.S., R and Ch, dissociated from an avian tubercle bacillus, A, have been described. They have different physical and chemical properties. The leukocytic response in S and F.S. is of acute type, while that produced by R and Ch variants is indicative of a chronic, healing tuberculosis. The tubercle formed by S is of an acute, "toxic" type; the F.S. more of a foreign body type, and that of R and Ch, relatively benign. The S variant is by far the most virulent and is closely followed by the F.S. type. The R and Ch variants are comparatively avirulent.

AUTHORS' SUMMARY.

TRANSFORMATION OF TYPE IN VITRO BY PNEUMOCOCCUS EXTRACTS. J. L. ALLOWAY, *J. Exper. Med.* **57**:265, 1933.

Pneumococcus extracts highly active in inducing the in vitro transformation of the specific types of *pneumococcus* have been prepared by dissolving S cells with sodium desoxycholate, precipitating the dissolved material in alcohol in which the bile salt remains soluble and extracting the precipitate in salt solution. Further purification of these active extracts has been attained by the removal of considerable inactive material by charcoal adsorption and by reprecipitation of the adsorbed extract in alcohol or acetone. The importance of using young cultures for extraction, and of preventing autolysis during the preparation of the extracts, is emphasized. Extracts prepared by the method described have been filtered through Berkefeld candles (V, N and W) without appreciable loss in activity, provided the reaction of the extract was slightly alkaline at the time of filtration. The purified and filtered extracts are waterclear and sterile by rigid cultural and animal tests. They have been heated to temperatures of 60 C. for thirty minutes without appreciable loss in their capacity to induce specific changes in type. And although they have generally shown definite decrease in potency after heating to temperatures above 80 C., some extracts have been found active even after an exposure of ten minutes to a temperature of 90 C. They have been completely inactivated by boiling. Relatively small amounts of extract have been effective when added to a broth medium containing normal serum or serous fluid. In this medium, R pneumococci, irrespective of their type derivation, have developed and thereafter retained all the type-specific characteristics of the encapsulated S cells from which the extract was prepared. The specific action of the extracts is discussed with reference to their transforming and antigenic properties.

AUTHOR'S SUMMARY.

CHANGES IN *BACTERIUM COLI* AND *BACILLUS MEGATHERIUM* UNDER THE INFLUENCE OF BACTERIOPHAGE. S. BAYNE-JONES and L. A. SANDHOLZER, *J. Exper. Med.* **57**:279, 1933.

Enlargement or swelling of the cells of *Bacterium coli* usually, but not always, precedes lysis. Some of the enlargement is an expression of increase of cell substance and is not altogether due to imbibition of water. Cells of early generations of *Bact. coli* enlarge to greater absolute and relative proportions than cells of later generations. Enlargement does not occur before lysis in *Bacillus megatherium*. The terminal stage of lysis of *Bact. coli* is explosive, occupying from one-half to seventh-eighths second. The terminal stage of lysis of *B. megatherium*

is a slow disintegrative process, extending over two to ten minutes. Bacteriophage inhibits fission of some cells, but does not stop the reproduction of other cells in contact with it. The genealogical records of six generations of cells of *Bact. coli* and of two generations of cells of *B. megatherium* indicate that bacteriophage may be transmitted through parents to the offspring which ultimately undergo lysis. Bacteriophage spreads by contact through a group of cells and also along paths determined by genetical relationships. A large amount of cellular debris remains after the lysis of the cells in both of these species of bacteria. This residue of material is in the form of irregularly shaped masses and granules. This material is not in solution at the time of lysis and appears not to be digested or hydrolyzed. Theories of the mechanism of lysis are discussed. It is suggested that reduction of surface tension of the cells may be an important factor in the mechanism of lysis.

AUTHORS' SUMMARY.

A STUDY OF THE BACTERIAL CAPSULE BY NEW METHODS. J. W. CHURCHMAN and N. V. EMELIANOFF, *J. Exper. Med.* **57**:485, 1933.

"Whatever the nature of the structures we have described we do not wish to be understood as suggesting that bacterial capsules necessarily resemble each other in any way. That they differ in chemical and biological properties appears certain. It is also known that they differ in the same organism under varying circumstances (e. g., the change produced in the capsule of *D. pneumoniae* III S by injection into the peritoneum of the mouse). It is to be expected that they will be found to differ in physical characteristics. The evidence we have presented should, we think, only be interpreted as justifying a reexamination of the whole question in which the problems raised will be attacked by means of methods not subject to some of the limitations of tinctorial technic. Such studies we now have under way."

MENINGOCOCCUS INFECTION. G. RAKE, *J. Exper. Med.* **57**:549 and 561, 1933.

Freshly isolated strains of meningococci present a number of characteristics which can be shown to differ not inconsiderably from those of stock strains long maintained on artificial mediums. Rough variants of the different types can be demonstrated, either arising spontaneously in vivo or in vitro, or evoked in the laboratory by the method described by Enders. Neither the freshly isolated strains—which are smooth—nor, in most cases, the rough variants of them are stable, both showing a tendency to pass over into the stock form or variant. The stock strains in the course of transformation from the freshly isolated strains show changes in morphology and cultural characteristics, and in viability in defibrinated blood.

The production of monovalent serums for agglutinin or precipitin reactions with freshly isolated strains of meningococci is described. Agglutination reactions with such serums can be carried out more rapidly, at lower temperatures and in lower dilutions, than with the standard monovalent serums prepared from stock cultures, while the results so obtained are more satisfactory owing to the relative absence of cross-agglutination.

AUTHOR'S SUMMARY.

THE CULTIVATION OF VACCINE VIRUS IN LIFELESS MEDIA. T. M. RIVERS and S. M. WARD, *J. Exper. Med.* **57**:741, 1933.

We have made ten attempts to cultivate vaccine virus in tissue extracts prepared according to the method described by Eagles and Kordi. Renal, testicular and chick embryo extracts were employed with a dermal strain of vaccine virus and with the Levaditi strain of neurovaccine virus. In no instance were we able to show that the virus multiplied in the extract mediums. Both of these strains of virus, however, multiplied in mediums containing bits of minced viable tissue. Furthermore, treatment of rabbit testicular tissue and chick embryo tissue in the manner described by Eagles and Kordi for the preparation of the extracts leaves some cells not only alive but capable of proliferation. Although the results of

our work are not in accord with those obtained by Eagles and Kordi, we offer no explanation for the discrepancy. Nevertheless, one cannot examine the results of our work recorded in the six tables without recognizing the fact that in the types of mediums used the presence of viable cells appears to be essential for the multiplication of vaccine virus. Rabbit testicular tissue and bits of chick embryos support the regeneration of the active agent more efficiently than does rabbit renal tissue.

AUTHORS' SUMMARY.

THE ETIOLOGY OF SPONTANEOUS CONJUNCTIVAL FOLLICULOSIS OF MONKEYS.
P. K. OLITSKY, J. T. SYVERTON and J. R. TYLER, J. Exper. Med. **57**:871, 1933.

In the bacteriologic study here reported, we undertook an investigation of the flora associated with spontaneous conjunctival folliculosis. Following the plan of Noguchi, monkeys and chimpanzees were inoculated with the different organisms recovered from affected tissues. By this means, we disclosed among the bacteria a new species, *Bacterium simiae*, which was found to be specifically active, in that it induced follicular reactions in the conjunctiva apparently indistinguishable from the disease as it occurs in nature. The specific action of the bacterium in animals is the more striking when it is compared with the innocuousness of other organisms isolated from cases of folliculosis, and also when considered in relation to the behavior of quarantined animals. While the disease arises spontaneously in stock animals, of over three hundred normal rhesus monkeys—these being isolated in lots of from ten to twenty and quarantined from six to fourteen weeks—not one has as yet shown folliculosis. With the significant exception already mentioned, the experimental disease was produced only when the inoculum contained either folliculosis tissue or cultures of the simian organism. Apart from these observations, the experimental results indicate that the bacterium has thus far been recovered only from cases of folliculosis and not from other forms of conjunctivitis or from normal tissues; the micro-organism has been isolated not only from affected conjunctivae of stock monkeys but also from the tissue of animals—macaques and apes—experimentally infected with the bacterium, and such recovered cultures have, in turn, been found to be specifically pathogenic in normal rhesus monkeys and chimpanzees. We may therefore postulate from this experimental study that an intimate relation exists between *Bacterium simiae* and spontaneous conjunctival folliculosis of simians.

AUTHORS' SUMMARY.

THE REACTION OF RABBITS TO SYPHILIS. P. D. ROSAHN, J. Exper. Med. **57**:907, 1933.

The results reported indicate that breed, race or family is a factor which significantly influences the response to infection with *Spirochaeta pallida*.

PATHOGENICITY OF PSEUDORABIES VIRUS ON ANIMAL PASSAGE. R. E. SHOPE, J. Exper. Med. **57**:925, 1933.

Pseudorabies virus, Iowa strain ("mad itch"), after passage through the brain of a guinea-pig, fails to produce infection in guinea-pigs when injected subcutaneously unless enormous doses are employed. Such virus is still pathogenic for rabbits when given subcutaneously and for rabbits and guinea-pigs intracerebrally. Comparison of the amounts of virus present in the brains of rabbits and guinea-pigs following fatal cerebral infection shows that the latter contain, per gram, only approximately one-tenth the amount of virus in the former. Comparing the resistance of the two species to subcutaneously administered pseudorabies virus, it has been found that rabbits are approximately one hundred times more susceptible than guinea-pigs. Over and above the working of these two factors, passage through the guinea-pig appears to achieve some actual attenuation of virus when tested by subcutaneous inoculation into guinea-pigs.

AUTHOR'S SUMMARY.

LOCALIZATIONS OF POLIOMYELITIS VIRUS IN CENTRAL NERVOUS SYSTEM.
H. K. FABER and L. P. GEEHARDT. J. Exper. Med. 57:933, 1933.

About four days after intranasal instillation, the virus of poliomyelitis establishes its initial focus, within the central nervous system, in the olfactory bulbs. It apparently reaches this structure through the axons of the olfactory nerves after primarily infecting the olfactory cells of the nasal mucosa. From this initial focus, the virus spreads (on the fifth and sixth days) through the olfactory tracts and their connections in the brain stem. A secondary focus in the hypothalamus is first established. From this, two main channels can be discerned: first, to the medulla; second, to the thalamus and midbrain. On the seventh day, the virus can first be detected in the spinal cord. It is widespread but is found in larger amounts in the cervical than in the lumbar segments. It is present in both the anterior and posterior horns, either in equal amounts or in slightly larger amounts in the posterior horn. It is also present in the intervertebral ganglions. The surmise is presented that the main route of infection of the cord is not from the medulla (which had been infected as early as the fifth day) but along the sensory tracts, presumably from the thalamus (spinothalamic tracts). Certain portions of the central nervous system were never found to contain demonstrable quantities of virus: These were the cortex of the frontal and parietal lobes (neopallium), and the cerebellum. The olfactory (archipallial) cortex (hippocampus) was only once found to contain virus: this occurred on the seventh day and in small amounts, and presumably had its source in the olfactory bulbs. The experiments of the seventh day suggest that virus had died out in areas previously infected (in the hypothalamus and thalamus, particularly), while continuing, apparently undiminished, in the midbrain and medulla, and spreading to the cord. These observations are in harmony with the general contentions of Fairbrother and Hurst that the virus is better adapted to survival in the lower portions of the cerebrospinal axis than in the higher. The conception here presented of the manner of entrance and routes of propagation of the virus of poliomyelitis in the experimental animal appears to be in essential agreement with the clinical and pathologic characteristics of the disease in man. Both the experimental disease and the disease as it occurs in man appear to present the features of an infection spread through nerve tissue only. It is unnecessary to assume that at any stage of its progress, during the incubation period or later, systemic or general extraneurvous infection is present.

AUTHORS' SUMMARY.

BACTERIAL INVASION FROM AREAS OF INFLAMMATION. V. MENKIN. J. Exper. Med. 57:977, 1933.

Trypan blue injected into an area of cutaneous inflammation induced by *Staphylococcus aureus* failed to drain readily to the tributary lymphatics when the dye was injected as early as one hour after the inoculation of the micro-organisms. Trypan blue introduced into an area of cutaneous inflammation induced by pneumococcus type I was retained in situ when the dye was injected about six or more hours after the inoculation of the bacteria. When an area of cutaneous inflammation was induced by the inoculation of a culture of *Streptococcus haemolyticus*, trypan blue injected into it drained readily to the tributary lymphatics for the first thirty hours following the onset of the inflammatory reaction. When the inflammation had lasted for forty-five hours or longer, the dye was fixed in situ and failed in most instances to reach readily the tributary lymphatics. The rapidity of fixation of the dye in the instances given would appear to depend on mechanical obstruction in the form of both a fibrinous network and thrombosed lymphatics or thrombosed lymphatics alone at the site of inflammation. As staphylococci, pneumococci and streptococci spread from the site of cutaneous inoculation primarily through lymphatic channels, the difference in the rapidity with which mechanical obstruction is set up in the areas inflamed by them will help to explain the differing invasive abilities of these pyogenic organisms.

AUTHOR'S SUMMARY.

ACUTE ENCEPHALOMYELITIS IN MONKEYS. T. M. RIVERS, D. H. SPRUNT and G. P. BERRY, *J. Exper. Med.* **58**:39, 1933.

No evidence was found to support the idea that vaccine virus placed in the cisterna magna is capable of producing an acute disseminated encephalomyelitis with perivascular demyelination either in normal or in partially immune monkeys. A testicular extract (Reynals' factor) did not induce vaccine virus to cause an acute disseminated encephalomyelitis in monkeys. Repeated intramuscular injections of brain extracts and brain emulsions into eight monkeys were followed in two instances by an inflammatory reaction, accompanied by demyelination, in the central nervous system. The exact relation of the injections to the disease of the nervous system is not clear. The combined action of vaccine virus and an emulsion of fresh rabbit brain did not lead to the production of an acute disseminated encephalomyelitis in monkeys that had received repeated intramuscular injections of emulsions and alcohol-ether extracts of normal rabbit brains.

AUTHORS' SUMMARY.

INFLUENZAL MENINGITIS. L. D. FOTHERGILL and J. WRIGHT, *J. Immunol.* **24**:273, 1933.

Influenzal meningitis is rarely seen in children under 2 months of age or beyond 6 years of age. About 80 per cent of the cases occur between the ages of 2 months and 3 years. Cord blood and the blood of infants under 2 months of age have considerable bactericidal power. With rare exceptions the blood of children between the ages of 2 months and 3 years has practically no bactericidal power. After 3 years, the bactericidal power gradually rises and appears to be permanent in adult life.

AUTHORS' SUMMARY.

INHERITANCE AS A FACTOR IN RESISTANCE TO AN INFECTIOUS DISEASE. M. R. IRWIN, *J. Immunol.* **24**:285, 297, 313, 319, 329 and 343, 1933.

1. A specific dose of a strain of *Salmonella enteritidis* injected intraperitoneally into members of an inbred strain of rats over a four year period produced a mortality of 93.5 per cent. The slight discrepancy from the reaction of an ideal control stock could not be explained on the basis of seasonal effects, environmental changes or by any measurable physical differences in the animals.

2. Selection within a random-mated stock of rats has been effective in isolating lines which continually produced an appreciable increase in the number of subjects resistant to a specific dose of a strain of *S. enteritidis* over the number that were found in the nonselected parental population. Considerable variation was noted among the survivors in their ability to transmit resistance to their offspring. The hybrid progeny from matings between survivors and members of a susceptible inbred race showed a greater resemblance in mortality to that of their resistant parents than to that of the susceptible parental strain. Offspring from matings of hybrid survivors to members of the susceptible strain, and inter se, gave further evidence that hereditary factors were in a large part responsible for the resistance displayed in the selected stocks. The genetic factors operative in the experiments were seemingly multiple, presumably cumulative in effect, and some were at least partially dominant over those making for susceptibility.

3. In an analysis of the reaction of a population to an infection, it is of the utmost value to determine whether or not the average is typical of the set. Should a critical examination reveal that the underlying probability for the event is not common for all of the subdivisions, but instead varies from subset to subset, it is reasonable to conclude that the causes of the deviations from the normal distribution lies within the subsets themselves. In such a case the average should be used simply as an explanatory figure, and not as representative of the set as a whole. Granting a reasonable degree of control of the environmental factors in these experiments, and also that there was uniformity in behavior between successive progenies of particular matings, the most reasonable conclusion would be to attribute

the differences in mortality between the subsets in large part to hereditary factors. Examples given in this article, combined with others previously reported, show clearly the variation one may anticipate between survivors in their ability to pass on factors for resistance to their offspring. Also, data have been given which set forth the variation in mortality which may be encountered in the progeny from a single male mated with various females.

4. Genetic and immunologic tests gave no indication of an influence of passive immunity in the experiments. The progeny from either carrier or noncarrier parents tended to be resistant only if so determined by their line of descent. There was no difference in the proportions of carriers within the surviving litters of carrier or noncarrier parents.

5. The weight in itself of the host animals cannot be considered as having contributed more than a minor part in the differences in mortality between the strains. The stock of the latest average weight at injection showed the greatest proportionate number of resistant animals. The determinative influence of the weight on the variation in mortality within the various strains was variable, with a tendency in each for a lower mortality to be associated with the litters of greater weight.

6. (With T. P. Hughes.) The whole blood of rats from two inbred strains highly susceptible to infection with *Salmonella enteritidis* showed little or no bactericidal activity toward this organism. Those subjects whose blood showed varying degrees of bactericidal activity were, on experimental infection, approximately equally distributed in surviving and nonsurviving groups.

AUTHOR'S SUMMARIES.

SEROLOGIC AND CULTURAL STUDIES OF MENINGOCOCCI, WITH SPECIAL REFERENCE TO TYPE V. B. E. SEGAL, *J. Infect. Dis.* 52:1, 1933.

Of the hundred strains of meningococci studied, thirty-six strains by agglutination and absorption tests were found to be type I, ten strains type II, twenty type III and twelve type IV. An indirect method of classification was resorted to in five cases. Rabbits were immunized with each of the strains, and the agglutination and absorption reactions of the homologous antisera were studied. Four were found to be of type IV and one of type III. Seventeen strains were found to differ serologically from any of the known types of meningococci. They have been shown to form a separate group distinguishable from the Gordon type strains by their agglutination and absorption reactions. The cultural and biochemical reactions of these seventeen strains I do not consider as sufficiently distinct to warrant their being placed apart as a new species. A fifth type is proposed for this group of seventeen strains, since the four existing Gordon types are differentiated purely on the basis of serologic differences. The seventeen strains forming a fifth type of meningococcus were all isolated from the spinal fluids in cases of clinical cerebrospinal meningitis occurring in the Chicago epidemic of 1928, in which all the four known Gordon types were encountered.

AUTHOR'S SUMMARY.

RELATION OF GASTRO-INTESTINAL POISON TO OTHER TOXIC SUBSTANCES PRODUCED BY STAPHYLOCOCCI. O. C. WOOLPERT and G. M. DACK, *J. Infect. Dis.* 52:6, 1933.

The method of the production of staphylococcic toxin on semisolid medium under partial carbon dioxide atmosphere has been applied to several strains of *Staphylococcus aureus* from food poisoning and other sources. By this method it has been possible to prepare powerful staphylococcic gastro-intestinal poisons which when fed to rhesus monkeys consistently caused symptoms of food poisoning similar to those seen in man. This enterotoxic substance appears to be distinct from the hemolysin, dermatotoxin and killing toxin found in such preparations. Two strains studied produced all of these toxins; one produced none and one strain

yielded no gastro-intestinal poison but large amounts of the other toxins mentioned. The gastro-intestinal poison was more resistant to heating and to adsorption than the other toxins, and was not neutralized by antiserum effective against the others. However, in no case was this food poison produced without the production of these other toxins, and whenever food poison was formed there seemed to be a rough correlation between the amount of food poison and the amount of these other toxins. The rhesus monkey was readily immunized actively against the effects of this poison, but attempts at passive immunization failed. In the use of the methods employed herein, a basis is afforded for the laboratory study of staphylococcic food poison.

AUTHORS' SUMMARY.

COLONY FORMATION OF *DIPLOCOCCUS RUBEOLAE* (MEASLES). R. TUNNICLIFF, J. Infect. Dis. **52**:39, 1933.

The strains of green-producing *Diplococcus rubeolae* isolated before and during the eruptive stage of measles have been found to belong to one immunologic group (opsonic test) and to produce a small, conical, depressed colony developing often into a hard, lobulated, adherent colony. The diplococci from the depressed conical colony were virulent for mice and produced an exanthem in rabbits. A variety of other greening colonies was also observed in the acute stage and during convalescence in measles, but opsonically their cocci did not belong to the measles group. Smooth convex, smooth conical and lacy-edged rough colonies, as well as minute G colonies, have been dissociated from colonies of *D. rubeolae*. The G type of colony was observed both before and after filtration through a Berkefeld V filter, but so far has not been recovered from Berkefeld N filters. Anhemolytic diplococci later producing greening have been recovered from Berkefeld N filtrates of *D. rubeolae* by serial plate cultures. So far neither the cocci from smooth and rough colonies dissociated from *D. rubeolae* nor those recovered from its N Berkefeld filtrates have been reverted immunologically or colonially to the depressed conical colony of *D. rubeolae*.

AUTHOR'S SUMMARY.

EXPERIMENTAL INFECTION OF MAN WITH A BOVINE STRAIN OF *BRUCELLA ABORTUS*. P. MORALES-OTERO, J. Infect. Dis. **52**:54, 1933.

A family consisting of three members volunteered to ingest for six weeks the infected milk of a cow suffering from infection with *Brucella abortus*. At the end of this period, none of the members had at any time shown any symptoms of the disease, and their blood cultures and blood agglutination tests remained persistently negative for *Br. abortus*. Two other volunteers inoculated, one through normal and the other through abraded skin, with the strain isolated from the infected cow's milk presented no symptoms of the disease, and their blood cultures were persistently negative for *Br. abortus*. In the blood of the latter of the two persons, a transitory positive agglutination of the organism (in a 1:40 dilution) was observed during the third and fourth weeks of the experiment.

AUTHOR'S SUMMARY.

A MEDIUM FOR THE ISOLATION OF *BACILLUS PERTUSSIS*. J. H. BAILEY, J. Infect. Dis. **52**:94, 1933.

A modification of the original Bordet-Gengou medium for the isolation and cultivation of *Bacillus pertussis* is given, consisting of the substitution of potato starch or potato flour for a portion of the potato in the original medium. The starch medium possesses the following advantages over the original medium: Batches are easily duplicated; it is easier to prepare, and *B. pertussis* appears in less time than on the original medium. The cultural characteristics of *B. pertussis* are the same on the starch medium as on Bordet-Gengou agar.

AUTHOR'S SUMMARY.

PROTECTIVE ACTION OF CAROTENE AGAINST INFECTION IN VITAMIN A DEFICIENCY. R. G. TURNER and E. R. LOEW, *J. Infect. Dis.* **52**:102, 1933.

Carotene is protective against bacterial invasion of the upper respiratory tract and the development of the pathologic systemic conditions accompanying vitamin A deficiency in rats. Carotene in olive oil has been stabilized for a period of four months or longer by the addition of hydroquinone to the solution. Both hydroquinone and quinhydrone act as inhibitors in the conversion of carotene to achrocarotene. Vanillin hastens this reaction. Solutions kept under nitrogen fade more rapidly than those in contact with air. Carotene therapy reduces the number of spontaneous suppurative lesions in the upper respiratory tract occurring in animals deprived of vitamin A; xerophthalmia is cured in 100 per cent and normal health regained in 74 per cent. The percentage incidence of bacteria in the nasal cavities and middle ear in animals fed active carotene is noticeably less than that encountered in animals given faded carotene or that in animals receiving no source of vitamin A.

AUTHORS' SUMMARY.

AGGLUTINATION EXPERIMENTS AS EVIDENCE OF THE DIVERSITY OF NONHEMOLYTIC STREPTOCOCCI. H. W. CROWE, *J. Infect. Dis.* **52**:192, 1933.

A method of cataloging the streptococci is briefly described. Four criteria are suggested for the determination of what should constitute different races of microbes: first, cultural and microscopic characters; second, disease-producing characters; third, special morphologic and biochemical characters, and fourth and most important for clinical medicine, serologic characters. Two of the last three must show definite differences. On the medium the formula of which is given in this article and by fermentation (criterion 3) individual streptococci show sharp differences. By agglutination tests with monovalent rabbit serums (criterion 4) it has been shown that certain streptococci, differing on chocolate agar but similar in fermentation, are heterologous in type. They are definitely distinct organisms, since two of three criteria are satisfied. By inference it may safely be assumed that the nonhemolytic streptococci are a large group containing many varieties. The differences between these varieties cannot reasonably be ascribed to mutation but are to be considered fundamental.

AUTHOR'S SUMMARY.

INVESTIGATION OF CERTAIN SYNTHETIC GLUCOSIDES FOR ANTIGENIC PROPERTIES. A. G. WEDUM, *J. Infect. Dis.* **52**:203, 1933.

Twenty-two glucosides of known composition were synthesized. These represented a wide range of structural formulas and solubilities and, in the condition in which they were used, a range of physical state from simple solutions through suspensoids and suspensions. The dispersing mediums were: water; saline solution; glycol; 10 per cent and 20 per cent alcohol; 0.5 per cent gelatin, and 0.5 per cent gelatin, 95 parts, plus acetone, 4 parts. These glucosides were tested for antigenic properties by injecting them into guinea-pigs for the production of precipitins, agglutinins and anaphylactins. In no instance were precipitins, agglutinins or evidence of anaphylaxis demonstrated. Pseudoprecipitation and pseudo-agglutination sometimes occurred.

AUTHOR'S SUMMARY.

EFFECTIVENESS OF STANDARD DIPHTHERIA ANTITOXIN AGAINST ALL TYPES OF DIPHTHERIA INFECTION. O. R. POVITZKY, M. EISNER and E. JACKSON, *J. Infect. Dis.* **52**:246, 1933.

Toxins derived from different types of *Bacillus diphtheriae* seem to be identical in their response to the standard diphtheria antitoxin. This is true whether the antitoxin is injected or whether it is developed in the animal body subsequent to immunization with toxoid. *B. diphtheriae-gravis* kills with a smaller number of organisms than *B. diphtheriae-mitis* and other strains. It probably produces toxin more rapidly in the human or animal body. The difference, however, is only in

degree, not in kind. The animals infected with gravis can be saved when the antitoxin is given early and in sufficient quantity. Hence it may be inferred that the present standard toxin and antitoxin are suitable for use in the prevention and cure of diphtheria occurring anywhere.

AUTHORS' SUMMARY.

ANTIBODIES IN PLACENTAL EXTRACTS. C. F. MCKHANN and F. T. CHU, J. Infect. Dis. **52**:268, 1933.

Protein material obtained from human placentas by extraction with a 2 per cent solution of sodium chloride and refined by precipitation with ammonium sulphate has been found in qualitative tests to contain substances, presumably antibodies, which neutralize diphtheria toxin, blanch scarlet fever rashes, neutralize the poliomyelitic virus and prevent measles in exposed susceptible patients.

AUTHORS' SUMMARY.

AGGLUTININS FOR PASCHEN BODIES IN EXPERIMENTAL VACCINIA. J. C. G. LEDINGHAM, J. Path. & Bact. **36**:425, 1933.

The development of agglutinins for Paschen bodies in the serum of the rabbit in response to inoculation with vaccinia virus is described. Data are presented in the form of charts.

STREPTOLYSIN. E. W. TODD, J. Path. & Bact. **36**:435, 1933.

Two different forms of streptolysin with distinctive characteristics may be prepared by cultivating hemolytic streptococci in serum broth and by omitting the serum from the culture medium. Serum streptolysin and serum-free streptolysin are equally hemolytic and equally antigenic; the antibody produced by inoculating either of the antigens into animals will neutralize serum-free streptolysin but will not neutralize serum streptolysin. In order to obtain serum streptolysin, which is resistant to neutralization by antistreptolysin, it is essential to bring the normal serum into contact with nascent streptolysin; the combining power of streptolysin which has been formed in the absence of serum is not altered by the subsequent addition of normal serum. The failure of antistreptolysin to neutralize serum streptolysin is not influenced by the time allowed for neutralization. When hemolytic streptococci are cultivated in serum broth containing a large quantity of antistreptolysin, active streptolysin is formed which does not combine with the antistreptolysin in the culture medium. The antigenic action of serum streptolysin is confined to the production of an antibody which fails to react with the antigen itself but which reacts with a closely related antigen.

AUTHOR'S SUMMARY.

THE PRODUCTION OF TOXINS BY CLOSTRIDIUM WELCHII. L. E. WALBUM and C. G. REYMAN, J. Path. & Bact. **36**:469, 1933.

As a medium for the production of *Cl. welchii* toxin, ordinary veal broth containing 1 per cent peptone and, for instance, 0.25 per cent dextrose (from p_H 7.6 to 7.8, in a paraffin-oil layer) is suited. The addition of fresh muscle, coagulated meat and similar substances is superfluous. Calcium carbonate ought to be admixed to neutralize the acids formed, but in order that this neutralization is sufficiently effective the distribution of the calcium carbonate must be kept up by continuous stirring during the entire growth (this method is utilized in the State Serum Institute, Copenhagen, for the production of toxin in practice). Under these experimental conditions the largest quantity of toxin was found after from ten to eleven hours of cultivation at 37 C., and after from twenty-one to twenty-four hours at 31 C.; the minimum lethal dose (injected in vivo into mice) varied between 0.015 and 0.03 cc. The addition of defibrinated horse blood or of phenanthrenchinnon to broth does not cause an enhanced production of toxin, nor does cultivation in broth boiled with liver offer any advantages. Whey with peptone gives the same

result as ordinary meat broth with peptone. Under the experimental conditions described the nonspecific acute poisonous substance (Wassermann, Kojima) is not formed in measurable quantities in the substrate containing up to 0.75 per cent dextrose. With a content of 2.25 per cent dextrose, however, it is produced in considerable quantities. The specific, thermolabile toxin has also an acute killing effect in larger doses (about from three to five times the minimum lethal dose). The toxin is most stable at pH 6. The proteolytic (albumose-splitting) enzyme has its action-optimum between pH 7 and 8. The gelatin-melting enzyme has an action-optimum at about pH 6, but having passed a minimum of between pH 7 and 8, the action of this enzyme ascends again with rising alkalinity. In view of the investigations made, the theory advanced by Dernby and Walbum regarding the production of the bacterial toxins has been applied to *Cl. welchii* toxin. The antitoxin-binding qualities appear to maintain themselves fairly constantly during the growth of the culture, notwithstanding the fact that the curve for the direct action of the poison gradually declines rather strongly.

AUTHORS' SUMMARY.

EXPERIMENTAL TUBERCULOSIS: II. SUPERINFECTIONS. A. BOQUET, *Ann. Inst. Pasteur* 50:5, 1933.

Dermal inoculation of virulent tubercle bacilli into tuberculous guinea-pigs after sensitivity to tuberculin developed resulted in a nodule the evolution of which was characterized by a shortened period of incubation. The state of hypersensitivity rapidly reached a maximum, but immunity followed more slowly. The lesions gradually appeared more quickly and became less grave, finally showing the necrotic and spontaneously curing lesions of Koch's phenomenon. The skin, membranes and subcutaneous tissues became refractory before other parts. Some inoculated areas, e. g., testicular tissue, at the time the skin was refractory showed progressive destruction by sclerosis or caseation. Refractory cutaneous tissues still allowed indirect involvement of lymph nodes. Somewhat similar results were obtained with the rabbit but these were less marked in degree. The change in resistance appeared to be concerned, among other things, with the presence of phagocytic cells and their increased lytic properties.

FROM AUTHOR'S CONCLUSIONS.

Immunology

THE ANTIBODY CONTENTS OF THE SERUM OF LEPERS. M. A. GOHAR, *Zentralbl. f. Bakt. (Abt. 1)* 122:516, 1931.

Nodules from patients with nodular leprosy were excised under strict aseptic precautions, triturated with saline solution and the supernatant fluid used in testing for complement-fixing antibodies and for agglutinins in the patient's serum. Eighteen samples of serum were employed, and none showed complement fixation or agglutinins against the leprosy bacilli in the triturated emulsions. The author concludes that further work must be done to prove that the leprosy bacillus is the only organism involved in leprosy.

PAUL R. CANNON.

Tumors

GLIOMAS IN THE REGION OF THE CAUDA EQUINA. JAMES W. KERNOHAN, HENRY W. WOLTMAN and ALFRED W. ADSON, *Arch. Neurol. & Psychiat.* 29:287, 1933.

Of the authors' twenty-six tumors of the region of the cauda equina, twenty-five have been studied anatomically. Of these, seven arose from the conus medullaris and eighteen from the filum terminale. In both instances the histologic structure was the same and resembled the similar gliomatous tumors of the brain or the spinal cord. The most frequent type was ependymoma (cellular and myxopapillary forms); much less common were astrocytoma (protoplasmic), astroblastoma, spongioblastoma multiforme (of Strauss and Globus) and oli-

godendroglioma. The usual clinical symptoms were pain and yellow spinal fluid (when the sciatica syndrome was bilateral).

G. B. HASSIN.

SPECIFIC ANTIGENIC QUALITIES OF CANCEROUS TISSUE. E. WITEBSKY and P. PÖPLAU, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **76**:82, 1932.

The ability of cancerous tissues to stimulate the production of cancer-specific antibodies varies. The variations in the result of the immunization depend primarily on the antigenic potency of the injected tissue and only secondarily on the qualities of the rabbits. On the other hand, the production of group-specific antibodies depends entirely on the individuality of the animal given the injection. Group-specific antibodies can be produced in an animal only if the corresponding antigenic substance is not present in the animal's own organs. Native and boiled cancerous tissues are about equally efficient. The claim of some authors that boiling is essential is disproved. By the addition of proper amounts of lecithin to the alcoholic extracts of organs or by the diminution of the dose of the antigen nonspecific reactions with noncarcinomatous tissues could be eliminated. Alcoholic extracts of normal intestines, which are known to react with cancerous antisera, may lose their ability to react in a nonspecific manner when properly prepared for the complement-fixation test (evaporation and resuspension in salt solution).

I. DAVIDSOHN.

CHEMICAL AND SEROLOGIC FRACTIONS OF CANCER EXTRACTS. ELISA MORELLI, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **76**:305, 1932.

The difficulty in the employment of alcoholic cancer extracts lies in the fact that they contain besides cancer-specific lipoids species-specific, group-specific and organ-specific lipoids and, finally, nonspecific lipoids. The group-specific lipoids can easily be removed by absorption with the proper red blood cells. The other antigenic fractions are difficult to remove and therefore are a source of serious mistakes. Lehmann-Facijs recently published a method of separating the cancer-specific portion from the others by means of fractional extraction. Morelli checked the work of Lehmann-Facijs, with negative results. Using the same technic, she was equally unsuccessful in trying to separate the Forssman antigenic fraction of human tissues from the group-specific fraction.

I. DAVIDSOHN.

PRIMARY CANCER OF THE LUNG AFTER CHRONIC ABSCESS. P. W. SSIPOWSKY, *Ztschr. f. Krebsforsch.* **36**:67, 1932.

The author describes a bronchiogenic cancer originating in the thickened wall of an old abscess cavity of the lung, which he infers was due to the chronic irritation of continued and attenuated infection. For comparison he also describes a somewhat similar case in which cancer developed from a tuberculous cavity. From the general similarity, he questions the importance of tuberculous infection per se as a factor in bronchiogenic cancer, and suggests that the element actually concerned is any irritation which might cause a chronic, productive, inflammatory process.

H. E. EGGERS.

COMBINED PULMONARY TUBERCULOSIS AND CARCINOMA. S. DERISCHANOFF, *Ztschr. f. Krebsforsch.* **36**:82, 1932.

Of ninety cases of pulmonary carcinoma observed at the North Caucasian University clinic during the years from 1923 to 1930, 16.75 per cent were associated with active tuberculosis. The lesions pursued independent courses, without evidence of any mutually restrictive effects. Tubercle bacilli could rarely be found in the sputum, since apparently the cancer shut off access of the organisms to it. Apparently old chronic tuberculosis predisposes to cancer by chronic irritation, whereupon the cancer so lowers the local resistance as to permit the infection again to become active. Ordinarily both types of involvement were found in the

same lung, with an absence of both in the other. Combined metastasis to distant organs was observed with some frequency. The cancer tissue may be destroyed, like normal tissues, by the infection, and may show tubercles of both the exudative and the productive type.

H. E. EGGERS.

EXPERIMENTAL CARCINOMA OF THE GALLBLADDER. L. I. GENKIN and J. D. DMITRUK, *Ztschr. f. Krebsforsch.* **36**:104, 1932.

The authors have attempted unsuccessfully to reproduce the experimental results reported by Kazama and by Leitch, in the production of cancer of the gallbladder by the introduction of calculi or other foreign bodies. Unlike the writers cited, who used guinea-pigs, Genkin and Dmitruk performed their experiments on rabbits, and although four years were allowed in the case of some of their animals, the only changes found, with two exceptions, were those of chronic inflammation. In the two that showed changes beyond this, the changes were of papillomatous or adenomatous character. As regards the priority of concretions or of cancer in this organ, the authors point out that proliferative changes may occur without the presence of stone, which is then likely to form as a result of stasis, infection or some other process. That cholecystitis is an important factor in the causation of cancer of the gallbladder they do not dispute, but they believe that the undue frequency of calculi in association with cancer is due to their frequent association with cholecystitis, while in some cases the stones may appear secondary to the malignant process.

H. E. EGGERS.

DIAGNOSTIC VALUE OF DIASTASE-ACTIVATING SUBSTANCES IN THE URINE IN CANCER. P. GEREB, *Ztschr. f. Krebsforsch.* **36**:115, 1932.

A diastase-activating substance has been reported in the urine of patients with cancer, which, while occurring in other diseases, does so less frequently than in malignant disease. Gereb studied this phenomenon with a view toward establishing its diagnostic applicability. He found that while the substance was present in the urine of 69 per cent of his patients with cancer, it was present also in that of 23 per cent of almost a thousand noncancerous controls, so that in his opinion, while it may have some indicative value, it can by no means be considered as the basis of a specific reaction.

H. E. EGGERS.

ATTEMPTED PRODUCTION OF RAT SARCOMA BY TOMATO JUICE. W. A. COLLIER and R. JAFFE, *Ztschr. f. Krebsforsch.* **36**:126, 1932.

The success in the induction of peritoneal sarcomatosis of the rat by repeated injections of unsterile tomato juice, or of organisms obtained from it, as reported previously by Bellows and Askanazy, was not obtained by these writers. The only changes observed in rats and mice after this treatment consisted in the appearance of inflammatory lesions. In an appended note, Askanazy states that after his and Bellows' initial success attempts at reproduction of the positive results have been unsuccessful.

H. E. EGGERS.

RARITY OF CANCER IN EGYPT AND ITS PROBABLE CAUSE. P. SCHRUMPF-PIERON, *Ztschr. f. Krebsforsch.* **36**:145, 1932.

The author previously reported on the incidence of cancer in Egypt, and found that it is only about one-tenth as frequent there as in Europe or America, even despite the occurrence there of cancer caused by Bilharzia, which constituted 13 per cent of the total cases of malignant conditions. Gastro-intestinal cancers are especially rare, this holding true even of Europeans living there. In his explanation of this disparity, the author expresses the belief that climatic and racial factors may be excluded, and he thinks that it is purely a matter of nutrition. The soil of Egypt has an unusually high content of magnesium salts, and it is

the resultant high intake of these, with a lessened ingestion of potassium salts, which he believes is responsible for the difference in the incidence of cancer.

H. E. EGGERS.

DIET AND CANCER. S. PELLER, *Ztschr. f. Krebsforsch.* **36**:217, 1932.

With reference to the belief that the alleged increase in cancer may be a matter of changed dietary, particularly of the increase in the consumption of meat that has been conspicuous in modern times, Peller summarizes the evidence against this view. If it were true, cancer should be outstandingly a disease of the more favored social classes, which is directly contrary to fact as demonstrated particularly in British mortality statistics, which show that the disease is commonest in the class of unskilled laborers and least frequent in the so-called upper class. It is true that cancer of the lower part of the gastro-intestinal tract is commoner in the latter class, but this would appear to be primarily a matter of the lower incidence in it of cancers higher up. While Peller recognizes alcoholic indulgence as a factor in the incidence of cancer, he finds that when this is combined with a high intake of meat, as in the landlord class, there is less cancer than among hired employees, such as waiters, in whom a high ingestion of alcohol is combined with irregular hours and sexual irregularity. It is in connection with cancer of the upper part of the alimentary tract that alcohol would appear to be most important. Finally, Peller doubts greatly that the increase of cancer as shown by mortality statistics is actual; he believes that it can be accounted for by altered age distribution and increased diagnostic accuracy, and that if there is a change, it is in the line of lowered incidence if these elements are considered.

H. E. EGGERS.

A LOCAL STUDY OF THE INCIDENCE OF CANCER. L. ENDRÖS, *Ztschr. f. Krebsforsch.* **37**:165, 1932.

The district of Zusmarshausen, in Swabia, offers unusual features which make it particularly suited for a local study of the incidence of cancer. The population has remained essentially unchanged in character during the last eighty years; there has been no industrialization with the associated economic upheavals; the region is one of very high mortality from cancer; the only change in habits is one of some interest in this connection—a rather radical improvement in the dietary, which originally was almost wholly vegetable and monotonous, with a deficiency of fat and protein and an excess of carbohydrate. It is now better balanced though still largely vegetarian. During the eighty years considered there has been no appreciable change in the mortality from cancer, though shorter periods show variable fluctuations. No relation of the incidence to the diet could be detected, nor was there any relation to the character of the potable water. This is true, too, of the character of the subsoil, but there did appear to be a relationship to the terrain in that localities near bodies of water showed a relatively high incidence.

H. E. EGGERS.

INHERITANCE IN CANCER. J. CHOLEWA, *Ztschr. f. Krebsforsch.* **37**:215, 1932.

Cholewa presents, along with a summary of the literature, several instances of apparent familial cancer. One of these concerns a mother with bilateral mammary cancer and a cancer of the uterus, who had two cancer-free sons and ten daughters, five of whom died of cancer, of the uterus or ovary and the breast. In the third generation there already have been three cases of cancer, of the uterus, breast and rectum (male). In the second family, both parents and four of eight offsprings have died of cancer, of the uterus in the female patients, and of the stomach in the male patients. In the third family, the great-grandfather died of carcinoma of the stomach. There were no cases of cancer among his ten children, but the next generation showed seven cases among eight persons, and so far there have been two in the last generation. The fourth case, which

he cites from unpublished data obtained from Professor Miculicich, concerns the apparent familial incidence of a neoplastic diathesis of mesenchymal tissue. Of three sisters, one had a uterine fibromyoma, one leukemia and one a uterine sarcoma.

H. E. EGGERS.

Technical

TWO USEFUL STAINING METHODS FOR THE HUMAN HYPOPHYSIS. F. B. KINDELL.
Bull. Johns Hopkins Hosp. 53:56, 1933.

The hypophysis is fixed for twenty-four hours in Zenker's fluid to which a dilute solution of formaldehyde has been added, or, more correctly, 90 cc. of Zenker's fluid without acetic acid plus 10 cc. of a 40 per cent solution of formaldehyde, the mixture being made immediately before use. The hypophysis should be cut into two or, better, into three blocks. Paraffin sections are made; these are treated to remove the paraffin and are then passed through graded alcohols; the mercury precipitate is removed in the usual way.

Fuchsin-Methyl Blue Method.—1. Wash in water.

2. Immerse for from fifteen seconds to two minutes, or longer, in a freshly prepared 1 per cent solution of potassium permanganate.

3. Wash in water.

4. Immerse for the same length of time as in 2 in a 5 per cent aqueous solution of oxalic acid.

5. Wash well, and follow by washing in distilled water.

6. Stain with a 5 per cent solution of aniline acid fuchsin at 60 C. Heat the stain gently on the slide until it steams, not boils, and allow to cool for from six to ten minutes. The dye can be poured back into the bottle and used again. In the preparation of this solution, Altmann's aniline fuchsin, not more than from 5 to 7 Gm. of fuchsin, will dissolve in 100 cc. of aniline water. The 20 Gm. of the usual formula is a waste of dye.

7. Wash in distilled water. If the section is too red, it may be decolorized somewhat by dipping once or twice in a 95 per cent solution of alcohol.

8. Immerse for from five to ten minutes in a 0.05 per cent aqueous solution of methyl blue (not methylthionine chloride, U. S. P.) until the basophil cells can be distinctly seen.

9. Differentiate quickly in absolute alcohol; clear and mount.

The eosinophil granules stain bright red; the basophil, deep blue.

Eosin-Methyl Blue Method.—Fix the tissues in Helly's fluid (a modification of Zenker's fluid). Zenker's fluid, solution of formaldehyde or Bouin's fluid may be used.

1. Wash in water.

2. Stain for from two to twelve hours in Mann's stain (1 per cent aqueous solution of eosin [water soluble, yellowish], 35 cc.; 1 per cent aqueous solution of methyl blue, 35 cc.; water, 100 cc.).

3. Wash in water.

4. Differentiate in a 95 per cent solution of alcohol containing 2 drops of concentrated ammonia water to 50 cc. of alcohol.

5. Wash in several changes of a 95 per cent solution of alcohol to remove the alkali.

6. Immerse for from thirty seconds to one minute in water acidified with a few drops of glacial acetic acid.

7. Wash in water, dehydrate quickly in alcohols, clear in xylene and mount.

The eosinophil granules stain red; the basophil, blue. The chromophobe cells and connective tissue are faint blue or almost colorless. The methyl blue in this method is an excellent nuclear stain.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, Oct. 12, 1933

V. H. MOON, *Presiding*

EXPERIMENTAL SYPHILIS OF MICE, RATS AND GUINEA-PIGS. JOHN A. KOLMER and CLARA C. KAST.

Mice, rats and guinea-pigs are susceptible to infection with *Spirochaeta pallida*. Local lesions at the site of inoculation are rarely produced. In these animals the infection remains latent over long periods, especially in the inguinal lymphatic glands and in the spleen. In mice the brain is also quite susceptible to invasion with *Spirochaeta pallida*, and the infection may remain latent in this organ over long periods. In view of the extreme latency and limited distribution of syphilitic infection in these animals, it seems that serologic tests for syphilitic infection are of no value.

EXPERIMENTAL AIR EMBOLISM. JOSEPH WOLFE and HAROLD F. ROBERTSON.

The amount of air necessary to produce death, when injected intravenously, differs with each animal and seems to be directly proportional to the size of the pulmonary artery and its branches. The lethal dose for a rabbit is approximately 0.5 cc. per kilogram, while for a dog it is 15 cc. per kilogram. For man it has been calculated that an amount of from 1,200 to 1,500 cc., or equal to man's vital capacity, may cause death. The speed of injection was of little importance so long as the period of injection was shorter than the time required for absorption. The injected air is found in the pulmonary artery and its branches. If the air is given in large amounts it may be found in the right ventricle, in the right auricle and even in the superior and inferior vena cava. In this manner the pulmonary circulation is partly or completely blocked. No air could be found in any of the other organs after sectioning them under water. At no time could we find that air, owing to gravity, will go against the blood stream and remain in the uppermost vessels if the animal is held in the upright position. From these experiments it appears that intravenous injection of a large volume of air may be expected to cause shock, dyspnea, cyanosis, slow pulse and convulsions. In cases in which a large volume of air is accidentally injected, it would be logical to aspirate the right ventricle since it is easily accessible. The amount of air which may be accidentally introduced during an ordinary intravenous injection is of no clinical significance.

EXPERIMENTS ON CHEMOTROPISM OF LEUKOCYTES. WILLIAM B. WARTMAN, MORTON McCUTCHEON and HAROLD M. DIXON.

In studying the phenomena of inflammation it is often difficult to decide whether a given effect is due immediately to bacteria and their products, or whether destroyed body cells and tissues have been contributory. Such a question arises in regard to attraction of leukocytes in inflammatory areas. Experiments were made in vitro to determine whether dead body cells (dried leukocytes) are able to attract live leukocytes. A clump of dried cells and a drop of fresh blood from the same person were spread between a slide and coverslip. Under the microscope the number of leukocytes making contact with the attracting body within an hour was counted and compared with the number which, distant from the attracting

body and wandering at random, made contact with an imaginary attracting body of the same size as the real one. The numbers obtained were on the average 10 and 2 per hour, respectively. Paraffin and bits of glass sometimes attracted and sometimes did not attract cells. A number of different micro-organisms attracted leukocytes vigorously. With *Staphylococcus albus*, an average of 21 leukocytes per hour made contact with the attracting body, showing that under the conditions of these experiments micro-organisms attract leukocytes more vigorously than dead body cells do.

Regular Meeting, Nov. 9, 1933

V. H. MOON, *Presiding*

PECULIAR NEPHRITIS ASSOCIATED WITH ACQUIRED SYPHILIS: REPORT OF A CASE. JOHN T. BAUER.

A colored man, aged 41, who stated that he had acquired syphilis sixteen years before and received little treatment, was admitted to the Pennsylvania Hospital with symptoms of chronic nephritis and hypertension. Hematuria and oliguria were never noted. His urine contained a moderate amount of albumin and moderate numbers of hyaline casts, leukocytes and undescribed crystals. The blood urea nitrogen rose rapidly over a period of six weeks from 69.5 to 180 mg. per hundred cubic centimeters, and the blood creatinine, from 7.2 to 13.4 mg. per hundred cubic centimeters. His reactions to a Wassermann test of the blood and to the Kahn test were strongly positive. Death resulted from uremia and terminal pneumonia.

The interesting changes post mortem were seen in the aorta and kidneys. An unsuspected saccular aneurysm was found in the ascending portion of the former, and in the latter extensive inflammatory changes unlike those usually seen in chronic nephritis were observed. The convoluted tubules were greatly dilated and contained granular debris and crystals of cholesterol. An interstitial infiltration of round cells existed chiefly about the tubules, occasionally in focal collections which bulged into the tubules but nowhere were those cells seen to break through the tubular epithelium. The collecting tubules contained a few hyaline casts. Although some of the glomeruli showed evidence of vascular change, they were not involved in the inflammatory process. Vascular changes were confined to the larger renal vessels, and little change was seen in the arterioles. No spirochetes were found.

From the descriptions and evidence presented by Rich (*Bull. Johns Hopkins Hosp.* 50:357, 1932), it was thought that the renal lesion represented syphilitic nephritis.

PARADOXICAL EMBOLISM: REPORT OF A CASE. JAMES TAYLOR.

A white woman, aged 45, was admitted to the Pennsylvania Hospital three weeks after a sudden onset of illness which began with chills, cough, blood-streaked sputum, sweating, pain in the epigastrium and weakness. She grew worse gradually, and on admission to the hospital the signs were suggestive of a resolving bronchopneumonia. A few hours after admission cyanosis accompanied by tachycardia, an extreme drop in blood pressure, sweating and delirium developed. The temperature began to rise, and a marked precordial activity was noted. Shortly afterward she died.

Necropsy revealed thrombi filling the left femoral and right internal iliac veins. Emboli were present in the small branches of the pulmonary and left renal arteries and in the splenic artery. Infarcts of some duration were seen in the lungs, left kidney and spleen. A long twisted embolus filled a patent foramen ovale and appeared to be on its way through the orifice. Massive pulmonary embolism was the immediate cause of death.

CORONARY OCCLUSION WITH ANEURYSM OF VENTRICLE: REPORT OF A CASE.
ALLAN D. WALLIS.

A case of aneurysm of the left ventricle is reported. A white man, aged 42, had suffered from dyspnea and dependent edema for two years following an acute attack of pain in the upper left side of the chest. Because of a transient loss of consciousness he was admitted to the hospital, where he remained in a state of advanced decompensation for six weeks until his death. Autopsy showed a recanalized occlusion of the left circumflex coronary branch with a large saccular aneurysm of the posterior wall of the left ventricle. The aorta showed marked arteriosclerosis without evidence of syphilis.

INTERAURICULAR SEPTAL DEFECT ASSOCIATED WITH MITRAL STENOSIS. W.
GRADY MITCHELL and JOHN T. BAUER.

A white man, aged 40, suffered for six years with dyspnea, cough, hemoptysis, precordial pain and terminal cyanosis. The cardiac findings were: (a) enlargement, especially of the left side along the left auricle and pulmonary conus, when the heart was seen by fluoroscopy; (b) a dense shadow moving from side to side in a slightly oval orbit in the region of the mitral valve observed on fluoroscopy; (c) electrocardiographic tracings showing partial auriculoventricular block; (d) an accentuated pulmonary second sound and a doubtful diastolic murmur at the base, and (e) a poorly defined systolic murmur over the pulmonic area.

At necropsy the heart was found to be huge, weighing 620 Gm. The right ventricle and auricle were greatly hypertrophied and somewhat dilated. The foramen ovale was closed, but an ostium primum remained beneath it. No ventricular septal defect existed. The tricuspid and mitral rings were formed. The tricuspid valves were well formed except for a wide zone of separation between the anterior and medial cusps. The mitral valve was fixed, firm and obviously stenotic. The cusp opposite the ostium primum showed marked calcification which extended from the ring into the myocardium and beneath the endocardium of the left ventricle and into the valve for a short distance. The chorda tendineae were thickened and shortened. Several atypical chords, present on the ventricular aspect of the mitral valve, were suggestive of Chiari's network. The area of calcification was associated with the formation of bone. The aortic valve and ring were much smaller than the pulmonic.

PERIARTERITIS NODOSA: REPORT OF A CASE. DAVID L. FARLEY and JAMES S.
TAYLOR.

A white woman, aged 35, was admitted to the service of Dr. Hollingshead, Cooper Hospital, Camden, N. J., on Oct. 3, 1932. Except for bronchial asthma for nine years she had always enjoyed good health. Her complaints were pain, numbness and swelling of both feet with prostration. She was found to have an eosinophilia of 72 per cent. Trichinosis was suspected, and a biopsy was made on muscle. This revealed the lesions of periarteritis nodosa. She died two and a half months later. Necropsy revealed generalized periarteritis nodosa.

OCCURRENCE OF COINCIDENT CALCULUS AND TUBERCULOSIS OF THE KIDNEY.
CHARLES R. TATNALL.

The occurrence of calculus in cases of renal tuberculosis is uncommon; the total number of such cases available is eighty-two, two of these from the Pennsylvania Hospital being reported for the first time. The incidence of calculus in tuberculous kidneys is variously placed at from 1 to 2.7 per cent. Tabulation of the cases shows them to occur mainly in patients in middle life without preference for either sex. It has been demonstrated that the tuberculosis may be the cause of the formation of a calculus, and it has been suggested that the irritation from the presence of calculi may predispose to tuberculous infection, but in most cases the coexistence of tuberculosis and calculus seems to be accidental.

(Complete reports of these cases will be published in the Ayer Clinical Laboratory Bulletin no. 13.)

Book Reviews

Diseases of the Heart Described for Practitioners and Students. By Sir Thomas Lewis, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Hon.D.Sc. (Michigan). Physician in Charge of Department of Clinical Research, University College Hospital, London; Physician of the Staff of the Medical Research Council; Physician in Chief (Pro Tem.), Peter Bent Brigham Hospital, Boston; Honorary Fellow, New York Academy of Medicine; Corresponding Member, Association of American Physicians and Interstate Postgraduate Medical Association. Price, \$3.50. Pp. 297, with 45 figures. New York: The Macmillan Company, 1933.

It is a good thing to have a book written by a competent author who is impelled to write because he has a message and who has a definite objective and a definite plan. In carrying out his purpose of writing not a book of reference but one that will help the practitioner to recognize and treat the more common diseases of the heart, Sir Thomas boldly breaks with tradition, discards old classifications and omits all that does not directly fit into his plan. He stresses not the laboratory but the bedside, not what others think but what he knows by experience, not anatomy but function, not theories but facts. When it is added that Sir Thomas has written in an orderly manner, with his usual clarity and conciseness and with the zeal of a missionary inspired to preach a new gospel, one may understand that the work is *sui generis*, one that is bound to attract wide attention and to elicit both extravagant praise and vehement criticism. In fact, the reviewer has already heard one competent physician declare it "the best volume on heart disease ever written," and another equally competent call it "rotten."

These diverging views can be understood. There are chapters that for their purpose are models. Those on angina pectoris and coronary thrombosis are word pictures with the clear lines of a steel engraving. The chapters on tachycardia, effort syndrome, rheumatic carditis, arteriosclerosis, syphilis of the heart and hypertension are most excellent. Lewis is not bound by tradition as to diagnosis, prognosis or treatment. If his experience shows him that percussion is of less value than palpation or roentgenograms in determining the size of the heart, he says so frankly. He freely admits that there are many gaps in the knowledge. He is strong in common sense. In no place is this common sense more in evidence than in his detailed outline of treatment, not only of the disease, but of the patient. And it is refreshing to hear his note of optimism as to many forms of heart disease.

The very plan of the work, with its commendable aim at simplicity, lays it open to criticism on the score of sins of omission. No two would agree as to what symptoms and signs, what drugs and what etiologic and pathologic features should be omitted. Thus the reviewer believes that his differential diagnostic paragraphs are among the most faulty in the book; others might not agree with this view. Such criticisms are inevitable, nor would they be avoided were Lewis himself or any one else to rewrite his book.

Some sins of commission are not so excusable. The author, usually dogmatic and announcing *ex cathedra* opinions without argument, at times adopts the attitude of an advocate to support some view to which he is partial. Shall this be called a defense reaction? He is belligerent and peppery when he discusses such questions as mitral regurgitation or the mechanical theory of heart failure. "Failure of compensation" is as the red rag to the bull. And in these arguments and invectives he is not always quite fair in stating the views of others. Nor is his position, as the reviewer sees it, always sound. He is not justified in ignoring—he practically does this—mitral regurgitation, and stressing alone stenosis, its murmurs and its effect on health. And why should he, as he virtually does, contend that because

with stenosis or coarctation of the aorta the heart does not give out early, the degree of obstruction is really of little moment? Nor is he alone in regarding the heart muscle and cardiac reserve as of prime importance; Martius, Krehl and others long ago wrote much on this topic.

The reviewer agrees with him as to the importance of the use by the practitioner of the unaided senses in reaching a diagnosis. But if the physician follows his advice—this is the tenor of the work—and uses the x-rays, electrocardiograph and sphygmomanometer only exceptionally, both the physician and the patient will often be deprived of useful knowledge to which they are entitled.

Moreover, there is an attitude of mind on the part of Sir Thomas that seems remarkable in one whose research work has taught him the value of accuracy and the worth of details. To take the position regarding the physician that he is to be content merely with essentials, that there are signs of disease which are interesting but he need not know them, that to judge of blood pressure by the unaided finger is good enough for him, and that after he graduates he will, of course, have nothing to do with the laboratory is not flattering to the practitioner; it relegates him to the ranks of mediocrity and classes him as nonprogressive. Fortunately all practitioners will not be satisfied to keep away from the laboratory and its methods, nor unthinkingly to accept opinions as correct merely because they are delivered by one so competent to give them as Sir Thomas Lewis. Many, most of those recently graduated, are well educated students, independent workers and thinkers. Sir Thomas is writing too much down to the level of the poorer practitioners—alas, there are many such. But is this attitude of the author the best one from the standpoint either of imparting information or of stimulating the reader to seek further?

One could go on praising and condemning his book. One could question whether undue emphasis has been laid on signs of heart failure outside the heart, on whether angina and congestion are really the only important features to be considered by the physician. Enough has been said to show that a work on a new model has been put forth, a work that is provocative, one that has merits that will be copied by later writers on cardiology as well as on other subjects, and one that has faults that should be avoided. It may interest the readers of a journal of pathology to know that this book, essentially clinical, contains an astonishingly small amount of pathology. What little there is, however, has been admirably selected, is sound and has an immediate value in explaining symptoms and disturbances of function. There is almost no consideration of microscopic pathology.

The format of the book is attractive. Several errors in typography and in the use of English can be corrected in later editions, which will surely be demanded.

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